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Distribution of Medical Schools in Japan

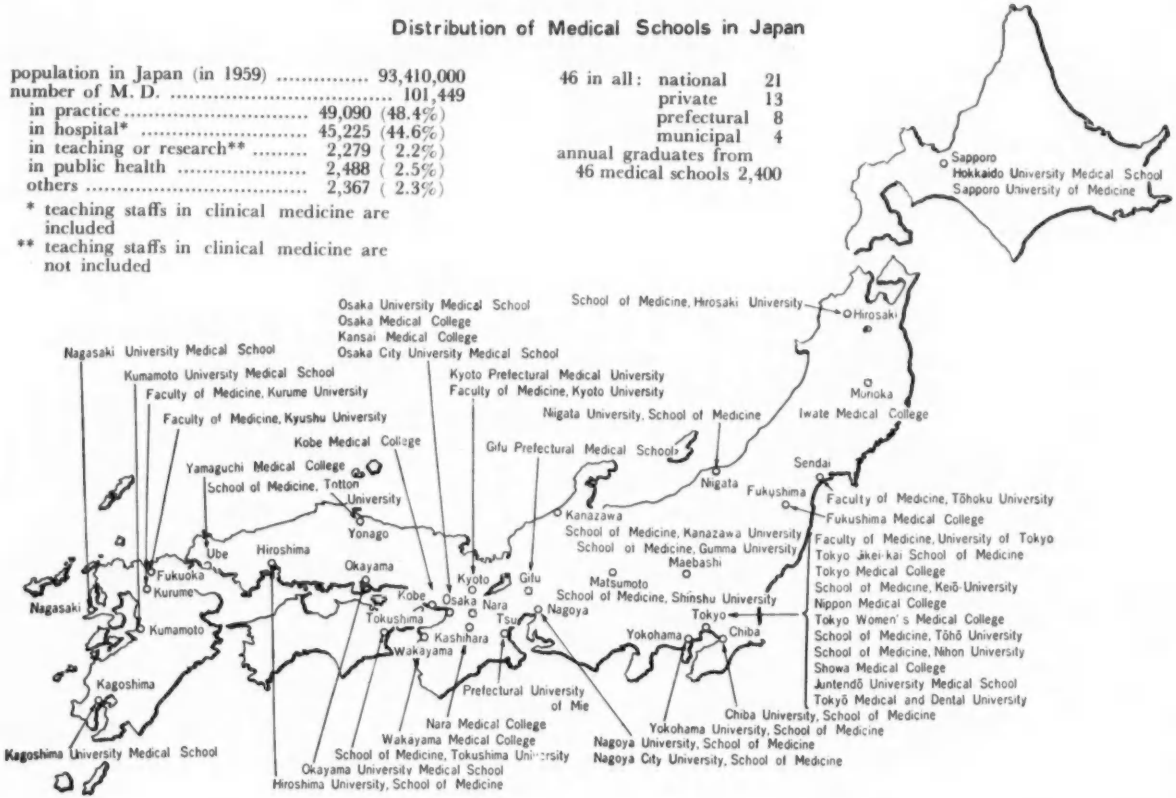
population in Japan (in 1959)	93,410,000	
number of M. D.	101,449	
in practice	49,090	(48.4%)
in hospital*	45,225	(44.6%)
in teaching or research**	2,279	(2.2%)
in public health	2,488	(2.5%)
others	2,367	(2.3%)

* teaching staffs in clinical medicine are included

** teaching staffs in clinical medicine are not included

46 in all: national 21
private 13
prefectural 8
municipal 4

annual graduates from 46 medical schools 2,400



Editorial

A New Look at an Old Problem . . .

ALTHOUGH over three hundred cases of chromaffin cell tumor have been reported to date in the medical literature, the correct diagnosis and localization of these tumors remains in many cases a challenging problem.

The fact that in earlier years the diagnosis of chromaffin cell tumors was quite often made at necropsy and that their presence is nowadays still often overlooked, is not only related with their very varying symptomatology and to the fact that a considerable percentage occur in cases of sustained hypertension, thus simulating "essential" hypertension, but is also due to the lack of reliable diagnostic tools.

Palpation of the tumor is rarely possible. Pheochromocytomas or adrenal chromaffinomas may be visualized by plain roentgenography in about 20% of cases, by intravenous or retrograde pyelography in about 35% of cases, and by retroperitoneal gas insufflation in about 50% of cases.

Furthermore, it is known that the various pharmacological tests—provocative (histamine, mecholyl) as well as blocking (phentolamine, benzodioxane)—may give false-positive or false-negative results. This disadvantage, together with the eventual occurrence of unwanted side-effects, considerably restricts their clinical value.

Ten years ago, Engel and von Euler observed that large amounts of catecholamines were excreted in the urine in two cases of surgically controlled pheochromocytoma. This finding has since been repeatedly confirmed. Moreover, a close correlation was generally found between the amounts of catecholamines excreted in the urine and the amounts present in the blood and in the tumor, showing that the excretion rate of the amines really parallels the activity of the tumor.

Using the photofluorimetric trihydroxyindole method for differential estimation of adrenaline and noradrenaline, we have carried out over one thousand estimations of urinary catecholamines between October 1957 and October 1960. In eight cases the presence of a chromaffin cell tumor could be diagnosed with certainty.

The urinary excretion figures of adrenaline and noradrenaline observed in 807 cases of hypertension, not due to a chromaffin cell tumor, and in the 8 cases of chromaffinoma hypertension, together with the weight and catecholamine content of the tumor in those cases in which the tumor could be assayed after surgical removal, are presented in Tables I and II.

Table II. Clinical Data and Urinary and Tumoral Catecholamine Content in 8 Patients with Chromaffin Cell Tumor

Patient No.	Age (Years)	Sex	Type of hypertension	Localization	Average urinary output in mcg./24 hrs		Catecholamine content of tumor in mg./Gm.		Tumor weight in Gm.
					Noradrenaline	Adrenaline	Noradrenaline	Adrenaline	
1	7	M	Paroxysmal	At site of right adrenal	188	33	—	—	—
2	17	F	Permanent + Paroxysmal	Between pubis and urinary bladder	724	12	0.67	0	40.6
3	26	F	Permanent	Thoracic sympathetic chain between Th_4 and Th_5 + at Th_{12} + 1 cm. above iliac bifurcation	264	7	0.50 0.96 —	0.12 0.15 —	3 15 1
4	21	F	Paroxysmal	At site of right adrenal	808	42	0.75	0.15	32
5	38	M	Paroxysmal	At site of right adrenal	644	19	0.59	0.02	20.6
6	46	M	Permanent + Paroxysmal	—	744	273	—	—	—
7	42	M	Paroxysmal	At junction of left ureter and urinary bladder	884	9	2.44	0	97
8	21	M	Permanent	At site of left adrenal	21	216	—	—	220

Table I. Urine and Urinary Catecholamine Output in 807 Hypertensive Patients

	Urine output (ml./24 hrs)	Noradrenaline (mcg./24 hrs)	Adrenaline (mcg./24 hrs)
Group 1: urine output of <400 ml./24 hrs			
Number of patients: 38			
Mean	277	11.56	2.92
±Standard deviation	76.4	6.32	2.42
Standard error of mean	12.56	1.04	0.40
Coefficient of correlation with urine output		0.73	0.58
Group 2: urine output of 400–800 ml./24 hrs			
Number of patients: 124			
Mean	618	21.41	5.58
±Standard deviation	113	14.39	1.16
Standard error of mean	10.15	1.29	0.10
Coefficient of correlation with urine output		0.60	0.68
Group 3: unine output of 800–1,200 ml./24 hrs			
Number of patients: 246			
Mean	1,040	26.37	6.80
±Standard deviation	119	16.55	4.44
Standard error of mean	7.59	1.05	0.28
Coefficient of correlation with urine output		0.55	0.60
Group 4: urine output of 1,200–1,600 ml./24 hrs			
Number of patients: 186			
Mean	1,437	32.04	8.41
±Standard deviation	136	19.48	6.52
Standard error of mean	9.98	1.43	0.48
Coefficient of correlation with urine output		0.59	0.52
Group 5: urine output of 1,600–2,000 ml./24 hrs			
Number of patients: 116			
Mean	1,753	37.07	9.60
±Standard deviation	109	22.09	9.21
Standard error of mean	10.12	2.05	0.85
Coefficient of correlation with urine output		0.72	0.47
Group 6: urine output of >2,000 ml./24 hrs			
Number of patients: 97			
Mean	2,500	45.82	12.47
±Standard deviation	558	28.72	7.84
Standard error of mean	56.63	2.91	0.80
Coefficient of correlation with urine output		0.57	0.64

As shown by the coefficients of correlation in Table I, a close parallelism holds between the diuresis figures and the catecholamine excretion figures in the various groups. Regression lines may also be derived from further statistical analysis of the data reported.

With regard to the chromaffin cell tumors of Table II, the highest excretion figures were observed in patient No. 6 in 24 hrs urine collected during and after an hypertensive attack, the excretion figures amounting to 1,588 mcg. / 24 hrs for noradrenaline and 432 mcg. / 24 hrs for adrenaline. In this patient, a voluminous pheochromocytoma, weighing 413 Gm. and containing 1.22 mg. of adrenaline and 1.85 mg. of noradrenaline per Gm. had been removed two and a half years prior to our first estimation of urinary catecholamines. Moreover, while the hypertension presented by this patient prior to the removal of the pheochromocytoma belonged to the permanent type, the recidive dealt with here is characterized by the occurrence of paroxysmal attacks of hypertension. Furthermore, the patient recently presented a tumor metastasis in a rib, which at biopsy showed the presence of chromaffin tissue and an adrenaline content of 3.5 mcg./Gm. whereas no noradrenaline could be detected.

The average excretion figures in patient No. 8 were preoperatively of 21 mcg./24 hrs for noradrenaline and 216 mcg./24 hrs for adrenaline, and postoperatively of 23 mcg./24 hrs for noradrenaline and 6 mcg./24 hrs for adrenaline. Apart from two pure adrenaline-producing tumors observed by von Euler in Sweden, we do not know of any other case in the literature in which enhanced excretion of adrenaline only was reported. This finding could unfortunately not be confirmed by assay of the tumor content since the tumor was not made available for photofluorimetric estimation.

It is obvious that the estimation of urinary catecholamines in the diagnosis of chromaffin cell tumors has some limitations in cases of paroxysmally secreting tumors. Between two attacks of hypertension, i.e. during a normotensive period, normal excretion figures of adrenaline and noradrenaline may be found, thus producing a false-negative result. In these cases it might be advantageous to rely on the estimation of methylated catabolites of adrenaline and noradrenaline: metadrenaline, normetadrenaline, and 3-methoxy-4-hydroxymandelic acid. After intravenous infusion of adrenaline or noradrenaline these catabolites are excreted in urine in amounts which are a 5- or 10-fold of the intact catecholamines. They may occur in increased amounts in urine as well during normotensive periods as during and after an attack in cases of paroxysmal hypertension due to the presence of a chromaffin cell tumor.

On the other hand, it is noteworthy to note that the quotient 3-methoxy-4-hydroxymandelic acid / catecholamines amounts to about 10 / 1 in the urine of patients with a chromaffin cell tumor, against a quotient

of 100 / l in the urine of normal individuals. This suggests a different pattern of metabolism of catecholamines, according to the amounts of catecholamines to be metabolized and the route of administration. Thus the intact catecholamines are excreted in much higher amounts after infusion of relatively high doses of catecholamines, as in cases of chromaffin cell tumor or after intravenous injection of exogenous catecholamines.

While the observation of excessive amounts of total catecholamines in the urine may give decisive proof of the presence of a chromaffin cell tumor, differential estimation of the neurohormones may give valuable information with regard to the localization of the tumor. Thus suprarenal chromaffin cell tumors usually release adrenaline as well as noradrenaline, whereas a chromaffin cell tumor secreting pure noradrenaline is usually located outside the suprarenals.

For a precise localization, the collection of blood samples, drawn by catheterization from different levels of the vena cava system, and the subsequent assay of these blood samples, may be most helpful. This was experienced in patients No. 2, 3, and 7, who presented a localization of chromaffinoma outside the adrenal glands.

It should be stressed, however, that this method presents definite pitfalls. Increased plasma levels of catecholamines may be found even in the absence of a tumor, due to the stress of the catheterization followed by a sympatho-adrenal discharge, thus producing false-positive results, whereas normal plasma levels of catecholamines may be found even in cases of sustained hypertension, due to an intermittent secretion of catecholamines from the tumor, thus producing false-negative results.

Attempting another approach, experiments have been designed in order to study the possibility of establishing a localization diagnosis of these tumors by scanning body areas for radioisotope concentrations after administration of a Cr^{51}-salt, which is expected to be selectively concentrated in normal and tumorous chromaffin tissue.

Thus nowadays, as well as fifty years ago, chromaffin cell tumors remain a real challenge to both experimental and clinical disciplines.

December, 1960

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Clinical and Phonocardiographic Study of Aortic Regurgitation

Hiroshi WATANABE, M.D. *and* Tsuguya SAKAMOTO, M.D.

An attempt was made in this study to correlate the phonocardiographic features with clinical findings in 105 cases of aortic regurgitation. The basic configuration of the aortic diastolic murmur is holodiastolic in nature and has a crescendo-decrescendo figure. Its time of accentuation, the grade of decreasing intensity and the loudness have good correlations with clinical findings of aortic regurgitation. The rapid filling and atriosystole frequently influence upon the configuration of the murmur. The "Q–1" interval shows the prolongation in severe cases, and there occurrs the "prediastolic murmur" in some instances.

THE first clue to the diagnosis of aortic regurgitation is based on the auscultation of the characteristic diastolic murmur, though other symptoms, signs and various examinations such as roentgenogram and electrocardiogram are essential for the evaluation of the clinical status. These findings, however, have no diagnostic significance in early stage of this disease because of their relatively late appearance in the course, while the murmur is the only and the first manifestation in the earliest stage because of its development coincide with this valvular involvement.

The characteristic diastolic murmur of this disorder has such a high-frequency component that the only phonocardiograph which has the superior characteristics of high-frequency recording is available for good registration. Recent advances in medical electronics have satisfied such requirement that the sufficient graphic recording of this diastolic murmur is now obtained without technical difficulties.

In this paper we present 105 cases of aortic regurgitation, occurring either as an isolated valve lesion or combined with the other valvular involvement, and investigate the phonocardiographic characteristics of aortic regurgitation. In addition, we report the correlations of the phonocardiographic findings and the clinical severity of this disease.

From the Second Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Tokyo.

Materials and Methods

Phonocardiographic study was made in a total of 188 cases with valve lesions accompanied by organic aortic regurgitation from October 1958 to September 1960 at the Second Department of Internal Medicine, Tokyo University Hospital. Among these, cases with rhythmic disturbances and holodiastolic musical murmur were excluded in this study. So, the phonocardiograms of 53 cases of aortic regurgitation (AI: 36 males and 17 females, aged from 18 to 69 with a mean of 44) and 52 cases of AI combined with tight mitral stenosis (CVD: 20 males and 32 females, aged from 10 to 60 with a mean of 29) were investigated.

The characteristics of the phonocardiograph used in this study and the methods of recording are the same as in the previous study.[1] The characteristic of high-frequency phonocardiogram (High PCG) of this apparatus is sufficient for the recording of the high-pitched diastolic murmur of aortic regurgitation.

The configuration of the diastolic murmur was investigated on the High PCG at the auscultatory maximal point of this murmur (usually at Erb's area), and the time of maximal amplitude (time of accentuation) of the murmur was examined in comparison with the time of the onset of the third sound recorded at the apex or Erb's area. The third sound was recorded at least on Low and/or Low Medium PCG in all cases with AI and in many of CVD. In the other few cases of CVD which had no definite third sound, the time of accentuation of the protodiastolic rumble was regarded as the time of the occurrence of the third sound except in one case, in which this time of accentuation was not discernible.

In order to display the decreasing grade in intensity of this murmur in the course of diastole, the interval between the points of maximal and its half amplitude ("Peak-1/2 Peak interval") was used.

The loudness of the diastolic murmur was determined by "intensity ratio" as follows:

$$\text{intensity ratio} = \frac{\text{amplitude of time of accentuation}}{\text{amplitude of calibration wave}}$$

Despite of many complicating problems and limitations concerning with the calibration method, definite correlation was noted between this intensity ratio and the grade used by Levine and Harvey[2] in high-frequency murmurs.

The "Q-1" interval was measured on the apical Medium PCG by the interval between the onsets of the Q-wave and the first major deflection of the first sound. The Low and Low Medium PCG were always used for the determination of the onset of the first sound lest we should interprete the accentuated aortic ejection component as the first major deflection of the first sound. This attention was especially needed in severe cases of AI in which the mitral component was diminutive.

In order to correlate the phonocardiographic findings with clinical status, the blood pressure and the chest roentgenogram were used as the indices of the clinical severity of aortic regurgitation. Blood pressure was measured immediately after the phonocardiographic recording, and the V point by auscultatory method was used for the diastolic blood pressure level. In 37 cases, the vessel tone was heard even at the level of 0 mm. Hg and this level was regarded as the

diastolic pressure level in such cases. Using the blood pressure level, the materials were divided into 3 groups as follows:

mild cases: diastolic pressure level greater than 61 mm. Hg and/or the amplitude of pulse pressure less than 100 mm. Hg,
moderate cases: diastolic pressure level between 41 and 60 mm. Hg and/or the amplitude of pulse pressure from 101 to 150 mm. Hg, and
severe cases: diastolic pressure level less than 40 mm. Hg and/or the amplitude of pulse pressure greater than 151 mm. Hg.

Validity for the judgment of the severity by blood pressure measurement in aortic regurgitation will be commended later.

The cardio-thoracic ratio was measured in the group of AI excepting 4 cases which were not available for their roentgenograms, and its correlations with phonocardiographic findings were also investigated.

A "T" test was performed to each correlation for analysing its statistical significance.

Results

I. *Configuration of the diastolic murmur.*

In 46 (86%) out of 53 cases of aortic regurgitation (AI) and 51 (98%) out of 52 cases of aortic regurgitation complicated with mitral stenosis (CVD), the configurations of the murmur showed the clear-cut crescendo-decrescendo figure. In the other 8 cases, the configurations were seemingly decrescendo, but all these were accompanied by the wide and/or musical second sound or musical quality at the beginning of the murmur (Fig. 1 A and B).

A) Time relationship between the time of accentuation and the onset of the third sound (Fig. 1).

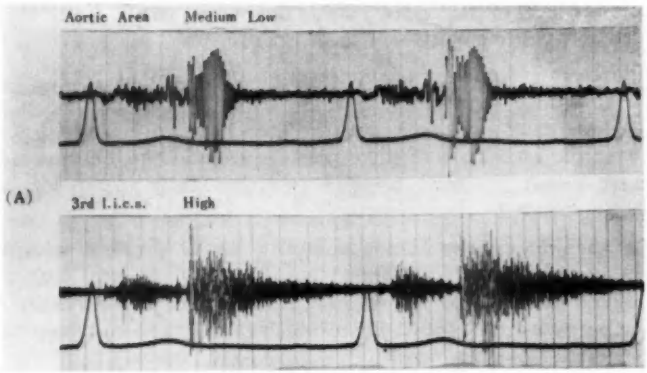
The time of accentuation of the murmur was different in each case. Comparing the time of accentuation with the onset of the third sound, 3 types were recognized as follows:

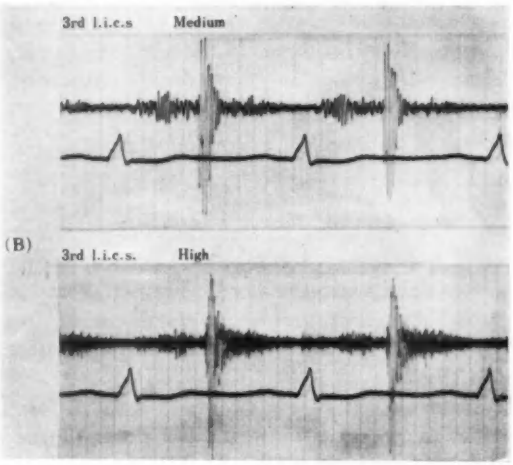
type "A": the time of accentuation occurred before the onset of the third sound (Fig. 1, C). The murmur of decrescendo appearance belonged to this type, because of the earlier appearance of the decrescendo part before the onset of the third sound.
type "B": this time of accentuation nearly coincided with the onset of the third sound (Fig. 1, D).
type "C": the time of accentuation occurred after the onset of the third sound (Fig. 1, E).

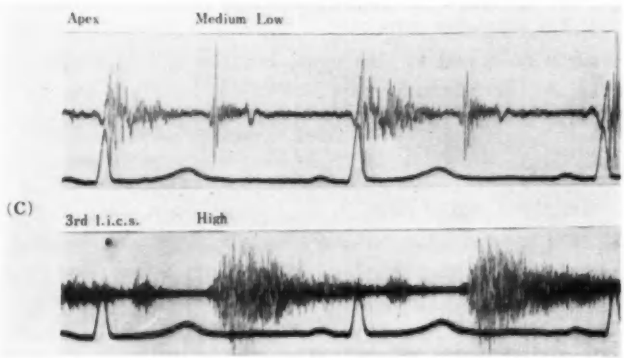
B) Correlations of the time of accentuation with clinical findings.

1) Correlation with diastolic pressure level (Fig. 2, Upper left):

Type "A" was observed in 80% of severe cases, while in moderate and mild cases type "B" or "C" was more frequently observed than type


Aortic Area Medium Low
(A)
3rd l.i.c.s. High


3rd l.i.c.s Medium
(B)
3rd l.i.c.s. High


Apex Medium Low
(C)
3rd l.i.c.s. High

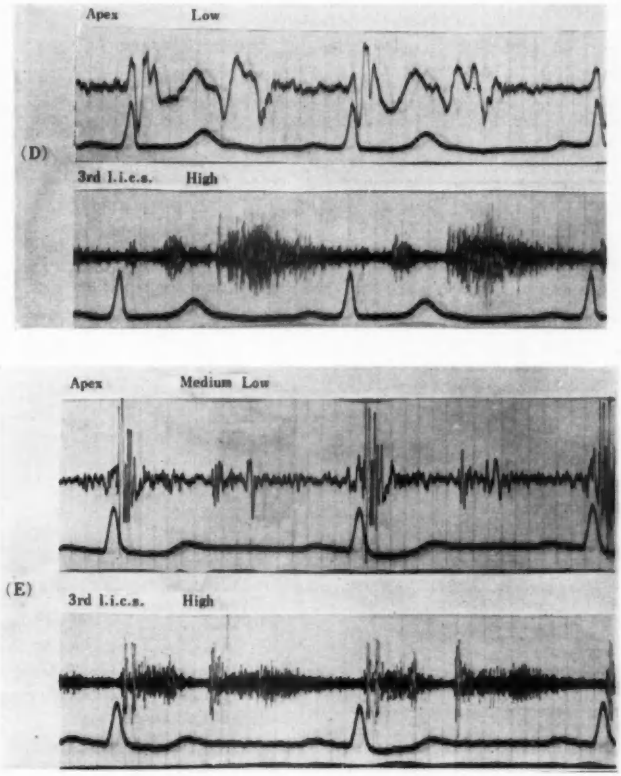


Fig. 1. Various configurations of aortic diastolic murmur:

A: musical murmur in early diastole followed by decrescendo configuration.
B: decrescendo murmur accompanied by wide and musical second sound.
C: type "A"—time of accentuation occurring before onset of third sound. The "prediastolic regurgitant murmur" is also observed (cf. Fig. 9).
D: type "B"—time of accentuation nearly coinciding with onset of third sound.
E: type "C"—time of accentuation occurring after onset of third sound.

Fig. A and B belong to the type "A" in their configurations of the murmur. Time interval between the vertical lines is 0.05 sec.

"A". The mean values of diastolic pressure level were 16 mm. Hg in type "A", 51 mm. Hg in type "B" and 50 mm. Hg in type "C", respectively. This results in a tendency that the diastolic pressure levels in type "A" are lower than those in type "B" and "C".

2) Correlation with the amplitude of pulse pressure (Fig. 2, Upper right):

A greater number of severe cases belonged to type "A", while in

moderate and mild cases type "B" and "C" were frequently observed. The mean values of the amplitude of pulse pressure were 140 mm. Hg in type "A", 80 mm. Hg in type "B" and 72 mm. Hg in type "C", respectively. These results were similar to the above-mentioned observations concerning with diastolic pressure level.

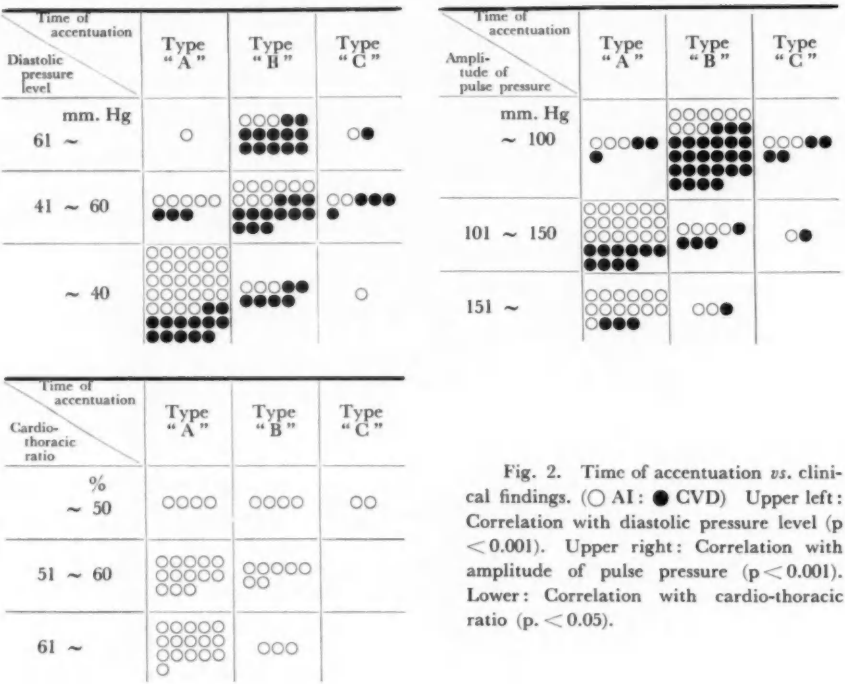


Fig. 2. Time of accentuation *vs.* clinical findings. (○ AI: ● CVD) Upper left: Correlation with diastolic pressure level ($p < 0.001$). Upper right: Correlation with amplitude of pulse pressure ($p < 0.001$). Lower: Correlation with cardio-thoracic ratio ($p. < 0.05$).

3) Correlation with cardio-thoracic ratio (Fig. 2, Lower):

This correlation was investigated in 49 cases of AI whose chest roentgenograms were examined. The cases with cardio-thoracic ratio greater than 61% almost always belonged to type "A", and then type "B" and "C" were frequently observed in the cases with the smaller ratio.

C) Observations on the decreasing grade in intensity of the diastolic murmur.

The murmur of aortic regurgitation has decrescendo figure after its time of accentuation. However, the decreasing grades in intensity after the time of accentuation are different in each case, as the grade is relatively abrupt in some cases, while gradual in others (Fig. 3). Using the "Peak–1/2 Peak interval", the decreasing grades in intensity were divided into 3 types as follows:

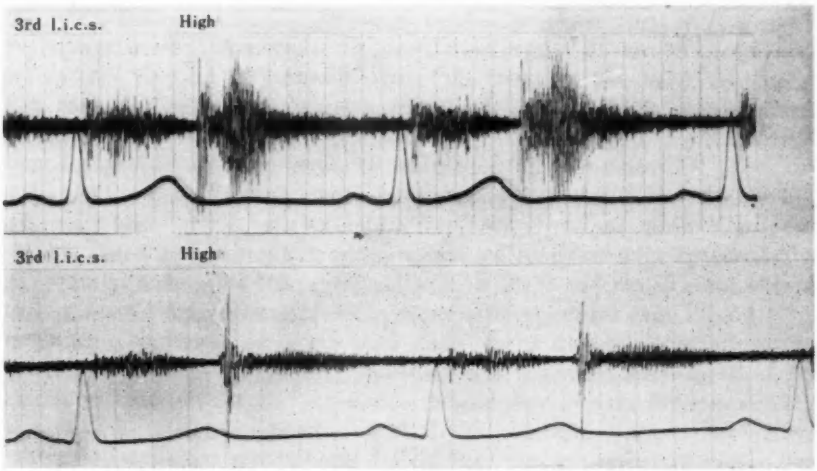


Fig. 3. Decreasing grade in intensity after time of accentuation. The murmurs decrease in intensity abruptly (upper) or gradually (lower) after time of accentuation.

type "a": "Peak–1/2 Peak interval" within 0.1″
type "b": ,, ,, 0.1 to 0.2″ and
type "c": ,, ,, more than 0.2″.

The correlations between these types and clinical findings were as follows:

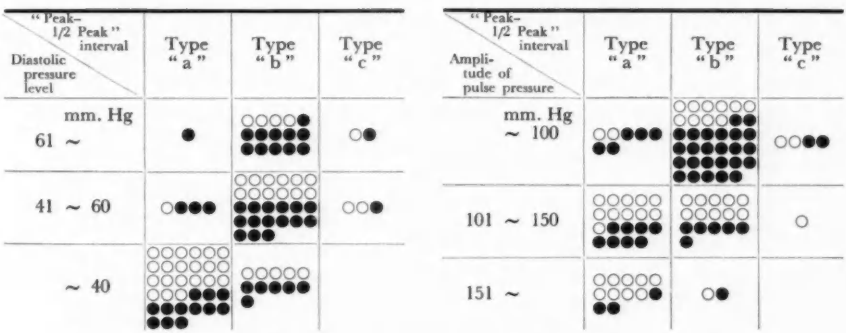


Fig. 4. "Peak–1/2 Peak" interval *vs.* clinical findings. Eight cases with decrescendo appearance of the murmur were excluded in these figures, because of the lack of maximal amplitude of the murmur. Left: Correlation with diastolic pressure level ($p < 0.001$). Right: Correlation with amplitude of pulse pressure ($p < 0.001$).

1) Correlation with diastolic pressure level (Fig. 4, Left):
A greater number of severe cases of aortic regurgitation had type "a",

while in moderate and mild cases type "b" and "c" were commonly observed. The mean values of diastolic pressure level were 12 mm. Hg in type "a", 53 mm. Hg in type "b" and 59 mm. Hg in type "c". This results in a tendency that the mean value in type "a" is lower than those in type "b" and "c".

2) Correlation with amplitude of pulse pressure (Fig. 4, Right):

In a greater number of severe cases, the configurations belonged to type "a", while in moderate and mild cases, type "b" and "c" were more frequently observed. The mean value of amplitude of pulse pressure was 133 mm. Hg in type "a", 84 mm. Hg in type "b" and 85 mm. Hg in type "c". These results were similar to the above-mentioned result concerning diastolic pressure level.

3) Correlation with the cardio-thoracic ratio:

No exact correlation was found.

D) Determination of the severity of aortic regurgitation utilizing the graphic configurations of the murmur.

Though the type "A", "B" and "C" or type "a", "b" and "c"

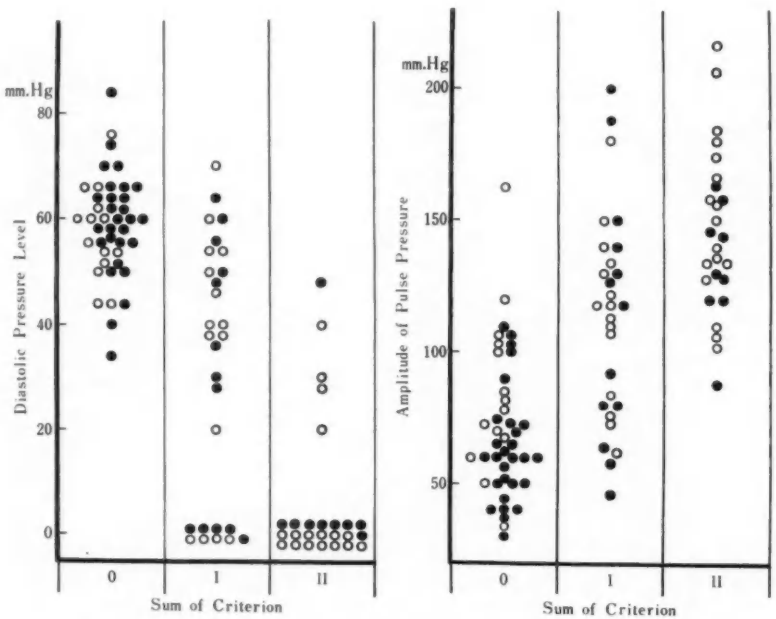


Fig. 5. Correlation of sum of the criterion with blood pressure. The cases represented in these figures are the same as in Fig. 4. Left: Correlation with diastolic pressure level. Right: Correlation with amplitude of pulse pressure. Details in text.

had significant correlations with blood pressure, these "A to C" and "a to c" types were independent in their manner in the correlations with the blood pressure. In any way, type "A" or "a" was most commonly observed in the cases with severe aortic regurgitation, thus it was postulated that these "A" and "a" types were significant criteria for the assessment of the clinical severity of this disease.

Using the combination of these 2 criteria, all cases are divided into 3 groups. The correlations between these groups and the diastolic pressure level or the amplitude of pulse pressure were demonstrated in Fig. 5. A greater number of the cases with 2 criteria belonged to the most severe stage of aortic regurgitation, and conversely, the cases without these criteria were commonly found in mild stage of the disease. The cases with 1 criterion fell midway between these 2 stages. The mean values of the diastolic pressure level and the amplitude of pulse pressure were 6 mm. Hg, 146 mm. Hg in the cases with 2 criteria, 32 mm. Hg, 110 mm. Hg in the cases with 1 criterion and 59 mm. Hg, 71 mm. Hg in the cases without any criterion.

II. *The other phonocardiographic findings.*

A) Duration of the diastoic murmur.

In 51 out of 53 cases with AI and 48 out of 51 cases with CVD, the

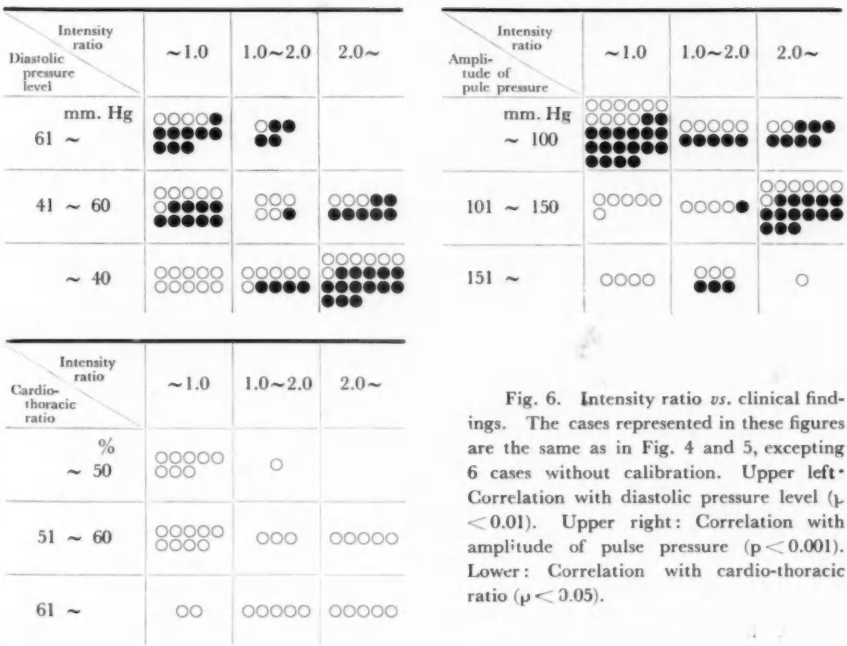


Fig. 6. Intensity ratio *vs.* clinical findings. The cases represented in these figures are the same as in Fig. 4 and 5, excepting 6 cases without calibration. Upper left: Correlation with diastolic pressure level ($p < 0.01$). Upper right: Correlation with amplitude of pulse pressure ($p < 0.001$). Lower: Correlation with cardio-thoracic ratio ($p < 0.05$).

diastolic murmur was "holodiastolic", while in the remaining the murmur disappeared in mid- or late diastole. In these instances, due to the extremely loud second sound, the amplification had not enough to registrate the diastolic murmur.

B) Correlations of intensity ratio of the murmur with clinical findings.

The murmur was divided by the loudness into 3 groups. The loudness of the murmur is expressed by the intensity ratios as follows:

loudest: intensity ratio greater than 2.0
loud: „ „ 1.0 to 2.0 and
mederate or faint: „ „ less than 1.0.

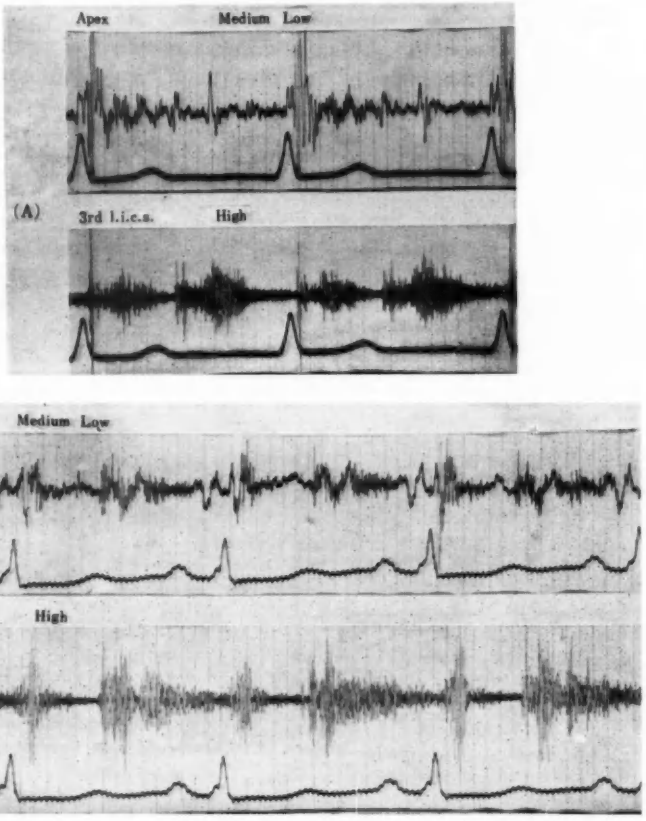


Fig. 7. Influences of rapid filling on the shape of aortic diastolic murmur: The rapid filling, expressed by the third sound, causes the transitional increase (A) or decrease (B) in intensity. Fig. B shows that this influence is variable in each cardiac cycle.

1) Correlations with blood pressure (Fig. 6, Upper):

In general, the more severe the case is, the louder the murmur with some exceptional cases.

2) Correlation with cardio-thoracic ratio (Fig. 6, Lower):

Similarly, significant correlation was noted. The cases with small heart were not accompanied by the murmur of greater intensity.

C) The influences of rapid filling and atrial contraction upon the configuration of the murmur.

The rapid filling, expressed by the third sound on the phonocardiogram, often causes the transitional increase or decrease in intensity of the murmur, and the influence upon the graphic configuration varies in each cardiac cycle and/or case by case (Fig. 7).

Atrial contraction also influences upon the appearance of the murmur in some cases. This influence is expressed by the transitional increase followed by the distinct decrease in intensity (Fig. 8).

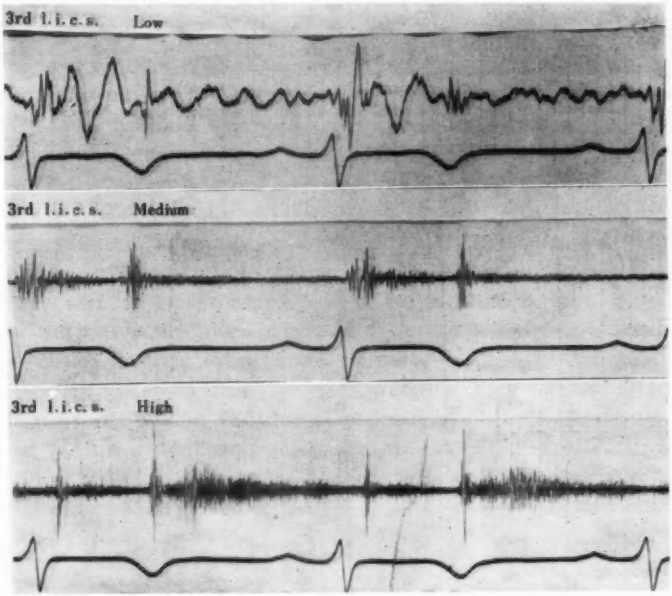


Fig. 8. Influences of atrial contraction on the shape of aortic diastolic murmur: At the period of atrial contraction, the murmur shows a transitional increase followed by the distinct decrease in intensity.

D) Timing of the onset of the murmur.

Before the appearance of the major vibrations of the second sound,

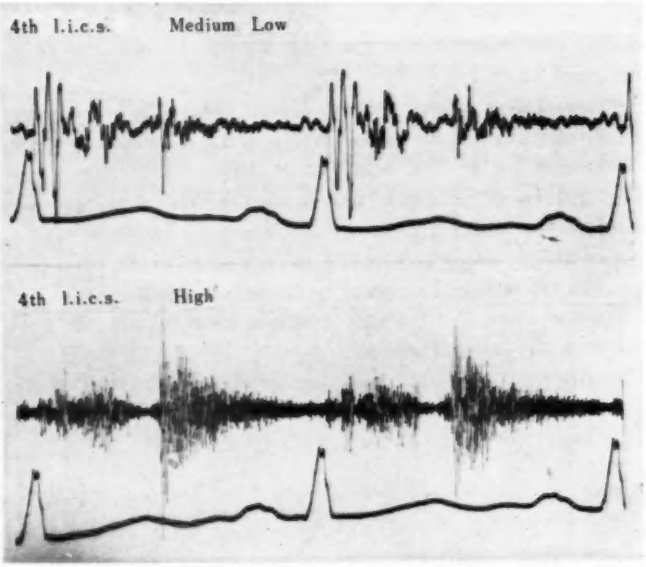


Fig. 9. "Prediastolic regurgitant murmur": Before the major vibrations of the second sound, a short crescendo murmur with small amplitude is recorded.

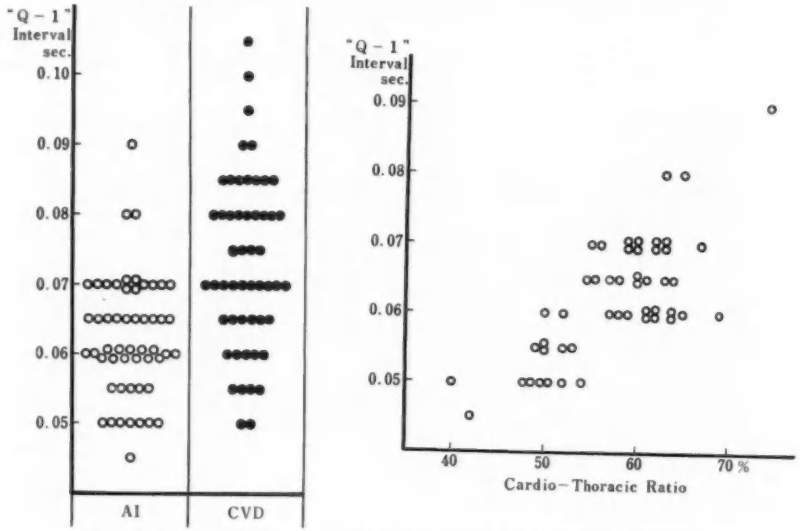


Fig. 10 (Left). Distribution of "Q–1" interval in AI and CVD.
Fig. 11 (Right). Relationship of "Q–1" interval to cardio-thoracic ratio in 49 cases with pure aortic regurgitation. Statistical significance: $r=0.74.$, $F_a=57.3$, $F_{47}^{1}{}_{(0.01)}=7.20$. A case of 0.09 sec. had Austin Flint murmur and no mitral involvement was found at autopsy.

there occurred a short but definite crescendo part of the murmur with small amplitude in 6 cases (Fig. 9). The duration of this crescendo part was about 0.025″ and this part was not preceded by the definite pulmonic second sound. The cases with such a "prediastolic murmur" belonged clinically and graphically to the severe stage of aortic regurgitation.

E) "Q–1" interval.

"Q–1" intervals of AI and CVD were shown in Fig. 10. Mean values were 0.062±0.009″ in AI and 0.073±0.012″ in CVD. "Q–1" interval of AI occupied a midpoint between normal adult and mitral stenosis, and significantly prolonged from the normal value (0.050±0.006″) which has already been reported by one of the authors.[1]

In 49 cases of AI whose roentgenograms were examined, a significant positive correlation was found between "Q–1" interval and cardio-thoracic ratio as shown in Fig. 11.

Comment

The validity to the use of the diastolic blood pressure level and the amplitude of pulse pressure as the indices of the clinical severity of aortic regurgitation—

As stated by Gorlin[3] and others,[4]-[8] there are many factors determining the diastolic blood pressure, such as vasodilatation or -constriction and heart rate, especially in the cases with congestive heart failure.[3] However, for the purpose of the clinical implication, it is well accepted that the lower the diastolic pressure level is, the more severe the degree of aortic regurgitation, as stated by Levine.[9] It is therefore justifiable to use the diastolic pressure level to evaluate the severity of the aortic regurgitation. With respect to the amplitude of pulse pressure, the same may be said. In the latter instance, moreover, the systolic pressure level also influences on the severity represented by the amplitude of the pulse pressure. In severe regurgitation, the systolic pressure rises as the compensation mechanism proper to this disorder. Consequently, this results in an increased amplitude of the pulse pressure in severe cases of aortic regurgitation, making the validity of the use of the amplitude as the index of regurgitation to considerable extent.

The cardio-thoracic ratio as an index of the degree of left ventricular enlargement in aortic regurgitation—

In aortic regurgitation, the increase in the cardio-thoracic ratio is considered to indicate the enlargement of the left ventricle, but in combined valvular disease this ratio is frequently influenced by both left and right cardiac enlargement. This ratio as the manifestation of the enlargement of left ventricle was exclusively employed in the cases with AI.

Discussion

The basic configuration of diastolic murmur of aortic regurgitation—

Generally speaking, the diastolic murmur of aortic regurgitation begins immediately after the second sound and decreases gradually in its intensity throughout the diastole, that is, it has the decrescendo character.[9)-12)] However, Wells and his associates[13)] and others,[14)-18)] using the phonocardiograph, demonstrated that in occasional cases the murmur had a brief crescendo part after the second sound. Moreover, McKusick[18)] received an impression that the crescendo-decrescendo pattern was most likely to occur in mild and moderate cases of aortic regurgitation.

As shown in this study, most cases showed the crescendo-decrescendo configuration. On the other hand, the decrescendo pattern was rather rare, in which it was always accompanied by the wide and/or musical second sound or musical onset of the murmur that may cover the brief crescendo part. From these observations, it is considered that the crescendo-decrescendo pattern is a basic configuration of the murmur of aortic regurgitation.

Though the exact mechanism producing the murmur is a complicated problem, the velosity of the flow may be very important in the generation of the murmur. It has been described that the velosity of the flow increases in proportion to the square root of the pressure difference across the aortic valve.[18)] Consequently, one of the most important factors influencing on the configurations of the murmur may be the time course of this pressure difference. In aortic regurgitation, the pressure difference across the aortic valve is small immediately after the aortic valve closure, and abruptly increases as left ventricular pressure falls steeply, and decreases gradually thereafter as left ventricular pressure reaches its diastolic level. Thus, this pressure difference during diastole has rather crescendo-decrescendo character than mere decrescendo. This fact may support our opinion that the diastolic murmur of aortic regurgitation is crescendo-decrescendo in its basic configuration.

The time of accentuation of the diastolic murmur and its clinical significance—

Several observations have been made on the timing of the maximal amplitude of this crescendo-decrescendo murmur. Holldack and Wolf[17)] observed that this brief crescendo part coincided with the time of dicrotic pressure rise in aortic root pressure pulse, and Wells and his coworkers[13)] described that the time of accentuation coincided with or occurred immediately after the *v*-wave of the jugular phlebogram. However, Luisada[19)] observed that the time of accentuation occurred simultaneously with the occurrence of the rapid filling. Of course, it is quite apparent that it must coincide with the rapid filling, if the shape of the murmur is determined only by the time course of the pressure difference across the aortic valve,

since the greatest gradient takes place in this time. The fact that the considerable number of cases had the time of accentuation coinciding with the third sound (Fig. 2) demonstrates the important influence of this pressure relationship upon the configuration of the aortic diastolic murmur. However, as the results obtained in this study, the time of accentuation did not always coincide with the rapid filling represented by the third sound on the phonocardiogram. In fact, the severe cases have frequently the earlier time of accentuation as compared with the time of rapid filling.

As described by Wiggers,[20)-22)] the steep pressure decrease in the aortic root mainly takes place before the atrial inflow in the experimentally produced severe aortic regurgitation. Possible cause of this pressure decrease is the large magnitude of the regurgitant flow in this stage. Such a large flow during this short period can not take place without the increased velosity of the flow or the reversible dilatation of the aortic ring which is encountered in the relative aortic insufficiency. Of course, the velosity of the flow is one of the most important factors dominating the intensity of the murmur, as stated by McKusick.[18)] However, it seems that such a high velosity of flow that causes the intensification of the murmur must not take place in the period before the atrial inflow, if one consider the behavior of pressure gradient across the aortic valve. The remaining factor causing the large magnitude of the regurgitant flow must be the reversible dilatation of the aortic ring. Such a large flow is the cause of the greater intensity of the murmur in the early diastole. Thus the early time of accentuation of the aortic diastolic murmur before the rapid filling period in severe cases is apparently caused by the great regurgitant flow during this stage. Such a dilatation of the aortic ring is frequently observed in the cases with enlarged heart as seen in severe hypertension. Therefore, this dilatation may be responsible for the fact that the enlarged heart of aortic regurgitation is frequently accompanied by the early time of accentuation.

The late appearance of the time of accentuation after the third sound is untenable by the above-mentioned explanations. However, as seen in the results of this study, the rapid filling or the atrial contraction frequently influences upon the shape and the loudness of the aortic diastolic murmur. In this instance the turbulence may be caused and continued in some extent by the collision between the regurgitant flow and rapid filling inflow. As a consequence, the murmur caused by this turbulence produces an additional distinct augmentation of the aortic diastolic murmur after the third sound, if the murmur preceding the rapid filling period is faint in its intensity. The fact that the late appearance of the time of accentuation is more frequently seen in mild cases may be understood by the above-mentioned explanations.

Another fact responsible for the difference of the appearance of the time of accentuation was found in the experimentally produced aortic re-

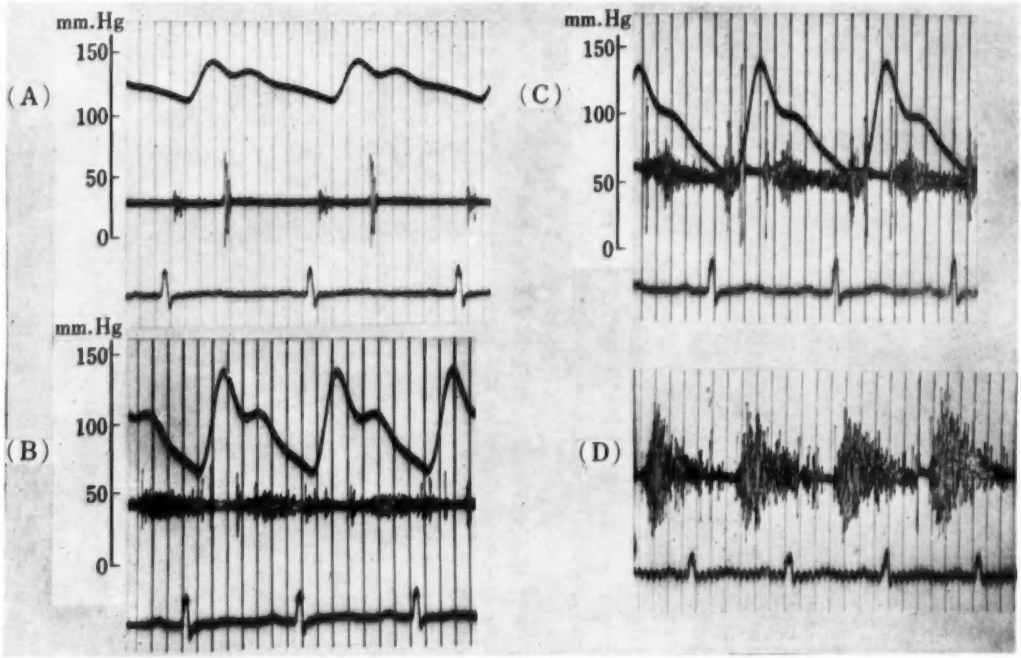


Fig. 12. Experimentally produced aortic regurgitation (case 3): Before (A) and after (B–D) the production of aortic regurgitation. B: Mild; lowered diastolic pressure level, dicrotic wave is still maintained clearly, spindle-shaped aortic murmur with late time of accentuation. C: Moderate; less marked dicrotic wave, time of accentuation approaches to second sound. D: Severe; marked increase in intensity, time of accentuation situates shortly after second sound. Autopsy finding of aortic valve: 3 perforations were noted (3 and 2 mm. in diameter, right anterior cusp; 4 mm., left anterior cusp). Thickened by hematoma, all, especially posterior, cusps were restricted in their movements to considerable extent.

gurgitation.* Fig. 12 shows that the larger the aortic leak is, the earlier the time of accentuation.

The decreasing grade in intensity of the murmur and its clinical significance—

Though the time of accentuation is an important phonocardiographic finding in aortic diastolic murmur, its decreasing grade in intensity is another significant feature in this disorder. The rapidly decreasing intensity after the time of accentuation in severe cases seemed to be explained by the same reason which described in the preceding item concerning with the time of accentuation. In severe cases, the regurgitant flow mainly takes place before the atrial inflow, because of the steep aortic pressure decrease before this time.[20)-22)] As the result, the volume of regurgitant flow, therefore the intensity of the murmur rapidly decreases after the time of accentuation. In mild cases, on the other hand, the reverse is true. Namely, the aortic root pressure decreases gradually throughout diastole,[20)-22)] resulting in the occurrence of the relatively greater regurgitant flow and the gradual decrease in intensity after the time of accentuation.

The synthetic assessment of the graphic configuration of the aortic diastolic murmur—

The time of accentuation and the grade of decreasing intensity are the most important graphic features of the aortic diastolic murmur. It is interesting that the severity of aortic regurgitation is easily assessable by the use of these 2 features. This fact appears to be of definite value in the phonocardiographic assessment of the severity of aortic regurgitation.

Other phonocardiographic manifestations—

Duration of the diastolic murmur: Several observations were made on the duration of the aortic diastolic murmur.[10),14),28)] Correlation of the duration with the severity of this disease has been observed by Holldack and Wolf,[17)] suggesting the duration might be longer in moderate cases and shorter in mild or severe cases. In our study, however, the murmur was holodiastolic excepting 5 cases. The disappearance of the aortic diastolic murmur in the course of diastole may be encountered in some of the advanced atrio-ventricular block, which is excluded in this study. In the cases with sinus rhythm, it is preferable that the murmur of the organic

* Five dogs weighing 10–15 Kg. were anesthetized with the combination of morphine hydrochloride (3 mmg./Kg.) and chloralose (40 mmg./Kg.). After bilateral thoracotomy, Lewis' phonocatheter was inserted into left ventricular cavity via left subclavian artery, and connected with multifilter system intracardiac phonocardiograph. Moreover, a metallic catheter, 2 mm. in diameter and 20 cm. in length, was inserted into aortic root via right common carotid artery, and was connected directly with Strain gauge manometer. By use of this metallic catheter, aortic valve was perforated or teared in various degrees. Intracardiac PCG was recorded simultaneously with ECG and the pressure pulse of the aortic root by the use of oscillograph. The results in 5 experiments were essentially the same as described in the text.

aortic regurgitation should be recorded throughout the diastole, if the sufficient amplification is available.

Intensity of the diastolic murmur: Wells and coworkers[18] stated that the intensity of the aortic diastolic murmur might decrease in severe cases. Mckusick[18] attributed the loudness of the murmur to the pressure difference across the aortic valve and not to the magnitude of the regurgitant flow closely correlated with the size of the aortic leak. If it might be so, it may happen that the larger the aortic leak is, the smaller the pressure difference and the fainter the loudness of the aortic diastolic murmur. Indeed, such a faint diastolic murmur is observed in some of the most severe aortic regurgitation, possibly due to the marked decrease of the velosity of flow which is proportional to the square root of the pressure gradient. However, such a thought is inconsistent with the much of clinical experience. In fact, Levine and Harvey[2] described that the intensity of the aortic diastolic murmur became louder in severe cases. In this respect, it may be considered that the velosity of flow is great in smaller leak but conversely the volume of the regurgitant flow is small, then in smaller leak the turbulence producing the murmur is relatively small in its energy. On the other hand, the greater leak causing the large volume of the regurgitant flow may produce the more sufficient energy to the production of the murmur as compared with the mild cases.[24] Levine's observation[2] and our result are consistent with these considerations.

Transitional changes of the shape and intensity of the aortic diastolic murmur caused by rapid filling and atrial contraction: The observations of these transitional changes are the interesting findings. Especially, the change caused by rapid filling is more or less so marked that it can be recognized easily on the High PCG without definite third sound in the maximal point of the murmur. The aortic musical diastolic murmur is frequently interrupted in this period (Fig. 1, A). This acoustic phenomenon may be produced by the collision of the 2 flows, as assumed from the observation by Wiggers and Maltby,[20] namely regurgitant flow from the aorta and rapid inflow from the left atrium. The fact that this change is variable in degree from cycle to cycle indicates that it may be produced by a delicate hemodynamic interference.

As described by McKusick,[18] atriosystole may influence upon the configuration of the aortic diastolic murmur. The transitional increase in intensity in our cases may be caused by the collision of the atrial inflow and regurgitant backflow in this period. The abruptly decreased intensity following this poriod may be caused by the sudden decrease in the pressure gradient across the aortic valve resulting from the abrupt rise of the left ventricular pressure in this period.

Relationship of the second sound to the onset of the aortic diastolic murmur: Commonly, this murmur has an onset coinciding with the second sound

or completely masking this sound.[2),5),10)-12),19)] However, the aortic diastolic murmur may occur somewhat before the second sound as seen in our severe cases with loud murmur. The possible reason for the genesis of this "prediastolic murmur" is based on the reversal of the pressure difference across the aortic valve slightly before the occurrence of the major vibrations of the second sound. The major deflection of the second sound is essentially produced by the tension of the semilunar valve after its closure. The time interval between the reversal of the pressure difference and the occurrence of the second sound is represented by the duration of short vibrations (the first phase[14)]) preceding the major deflection, which measured at the average of 0.025″ on the Low PCG,[25)] and corresponds to the duration of the "prediastolic murmur". In severe cases with loud murmur, therefore, it is likely that the aortic diastolic murmur may start immediately after the time at which the left ventricular pressure becomes equal to or less than the aortic pressure. Moreover, it is unlikely to regard this "prediastolic murmur" as the pulmonic second sound due to paradoxical splitting, because of the definite duration and the independence to the respiratory cycle. The McKusick's observation[18)] concerning the late systolic element of musical diastolic murmur on his spectrophonocardiogram may also be interpreted by the above-mentioned considerations.

"*Q–1*" *interval*: It failed to find the reports concerning the prolongation of "Q–1" interval in aortic regurgitation, but this prolongation is interesting and important finding in this involvement because of a positive correlation with the cardio-thoracic ratio representing the grade of left ventricular enlargement in this disease. Though many reports[1),26)-34)] have been published on the problem of the prolongation of "Q–1" interval, the exact mechanism of this prolongation in aortic regurgitation has not been clearly explained in this study. However, the positive correlation between the prolongation of "Q–1" interval and the degree of the left ventricular enlargement suggests that, as seen in hypertensive hearts,[1)] this prolongation is the objective reflection of the impending left heart failure or heart failure itself which will develop in the hearts of aortic regurgitation as an inevitable consequence.

Summary and Conclusions

The clinical and phonocardiographic study of aortic regurgitation was carried out with special reference to the various graphic characteristics of the diastolic murmur in 105 cases of aortic regurgitation. The phonocardiograph used in this study was suitable to registrate the high-frequency diastolic murmur characteristic to this lesion.

(1) The basic configuration of the aortic diastolic murmur was crescendo-decrescendo in its figure. In exceptional cases, the crescendo part

was obscure because of the widening and/or musicality of the second sound or musical onset of the murmur particularly in severe cases.

(2) In most cases of severe regurgitation, the time of accentuation of this murmur (the point of maximal amplitude) fell a midpoint between the second sound and the rapid filling period represented by the third sound. On the other hand, in moderate and mild cases, the time of accentuation frequently coincided with rapid filling period or later. Moreover, the decreasing grade in intensity of the decrescendo part was more prominent in severe cases. Namely, the severer the case is, the earlier time of accentuation and the more rapidly decreasing figure of the murmur are observed. This finding has much clinical use as the one of the objective judgment of the severity of aortic regurgitation.

(3) The loudness of the diastolic murmur showed some positive correlation with the severity of aortic regurgitation, though a few of severe cases had the decreased intensity.

(4) Principally, the aortic diastolic murmur was holodiastolic and sometimes had a short crescendo part before the second sound ("prediastolic murmur" of aortic regurgitation). The configuration of the diastolic murmur was more or less influenced by the rapid ventricular and the atriosystolic filling.

(5) The "Q–1" interval in aortic regurgitation showed a definite prolongation particularly with the enlargement of the heart.

(6) Detailed discussions were made on the above-mentioned phonocardiographic findings, and their clinical significances were discussed.

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Phonocardiographic Study on the Acute Rheumatic Carditis

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Repeated phonocardiographic examinations were made on 65 cases with initial attack of rheumatic fever. A total of 52 patients having cardiac manifestation were served as consecutive study. Authors present the phonocardiographic features in the early stage of rheumatic carditis correlating with the activity of the disease; in most instances significant murmurs, gallop rhythm and abnormal splitting of pulmonic second sound are coincident in acute phase. Among significant murmurs apical mid-diastolic murmur displays its reversibility. The E/M at apex or ratio of the duration of electrical systole (QT-interval) to that of mechanical systole (I-II interval in apical Medium PCG) varies with the degree of rheumatic activity. Increasing value of this ratio is parallel with rheumatic process. From these results presence of rheumatic activity would cause flabby or feeble state of myocardium which may also be an important factor in generating significant murmurs as well as actual "valvulitis".

THE most significant and often fatal manifestation of rheumatic fever is carditis. Its clinical recognition usually depends upon the detection of cardiac murmurs. But in general the evaluation of cardiac murmurs may be difficult, since they often occur in patients associated with tachycardia or co-exist as a functional murmur. Precise and objective cardiac findings and differentiation of various types and qualities of murmurs are essential for the diagnosis of active rheumatic carditis. Attempts to evaluate the clinical significance and to clarify the characteristics of cardiac murmurs in rheumatic fever by means of graphic method have been made during past 2 decades. Schwarzchild and Feltenstein[1] recorded the apical diastolic murmur due to acute valvulitis by phonocardiographic method in 1935.

Since Bouillaud's first description[2] (1835, 1840), the cardiac murmurs in rheumatic fever have been said to have changing and transient nature. Thus many arguments on the mechanism of the production of murmurs have also been discussed; presumably either acute valvulitis or myocardial

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damage or both (2 lesions) are responsible for the production of murmurs.

We present in this report phonocardiographic observation of 52 cases with initial attack of rheumatic carditis. The purpose of this study is to find the characteristics of phonocardiographic changes in early stage of this illness and to solve the problem of pathophysiology of the mechanical phenomenon in the rheumatic heart through correlations of the clinical data with those supplied by phonocardiographic and electrocardiographic findings.

Materials and Methods

Fifty-two children and adolescents who admitted to Tokyo Hospital because of rheumatic carditis were examined repeatedly. In addition to these cases, 13 patients whose manifestation was only migratory polyarthritis or chorea were also studied as a control group. A total of these 65 cases were presumed to be in their first rheumatic attack. During the observation, recovery from acute attack occurred in all patients with or without cardiac involvement but later 7 cases of carditis died of repeated reccurrences.

Sixty-five cases with rheumatic fever were divided into 3 groups according to their conditions obtained from clinical data. Group 1: patients with moderate rheumatic activity and under moderate limitation of physical activity or class III in functional capacity. Group 2: patients with slight rheumatic activity and under class II in functional capacity. Group 3: patients with slight to moderate rheumatic activity but without recognizable cardiac involvement (control group).

The rheumatic activity was estimated by data obtained from physical, laboratory, electrocardiographic and roentgenographic examinations. In most cases phonocardiograms were taken in series whenever there was a change in either rheumatic activity or auscultatory fiinings. In some cases sound tracings were made only at their acute and convalescent phase.

The sound tracings were recorded by means of the Multichannel Phonocardiograph having 5 distinct frequency characteristics (Low, Medium-low, Medium, Medium-high, and High ranges), with the patient in the supine position, holding the breath at expiration. Tracings were recorded subsequently from Low (No. 1) to High (No. 5) at a film speed of 10 cm. per second (at times, 5 cm. per second). Recording was made at the apex, pulmonic area, aortic area, tricuspid area and the fourth left sternal border. Lead II of electrocardiogram was recorded simultaneously. At the same time, 12 leads electrocardiogram and P-A roentgenogram of the chest were taken, and from the latter "cardio-thoracic ratio" was measured to determine the cardiac enlargement. On the electrocardiogram, prolongation of atrioventricular conduction, deformity in QRS-complex, deviation of ST-segment, change in T-wave and prolongation of QT-interval or increase in corrected QT (QTc) were analysed.

According to Mitsuya et al.,[8] lengthening of QT-interval was examined by comparing with the duration of the mechanical systole which obtained through following procedure: a distance between the beginning of central phase of the first heart sound and that of the second heart sound in apical "Medium"

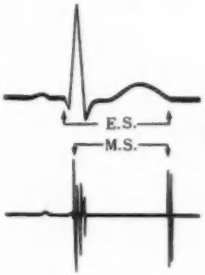

Fig. 1. Schema of phonocardiogram at apex.
E.S.: duration of electrical systole, M.S.: duration of mechanical systole.

phonocardiogram (Fig. 1). This ratio was tentatively expressed as "apical E/M" in percentage. Conditions affecting the duration of electrical systole other than rheumatic process such as digitalis effect, presence of congestive failure and pericarditis with effusion etc. were excluded from the calculation of "apical E/M". Duration of mechanical systole was not measured when there was a replacement of the first or second heart sound by murmur.

Results

Phonocardiographic findings in active carditis were very fluctuating or changing in nature.

I. Evolution of Abnormal Heart Sounds and Murmurs.

A. Abnormalities in Heart Sounds (Table I, Fig. 2, 3, 4)

In group 1 which included 43 patients, gallop rhythm occurred in 26 (60.4%) and abnormal splitting of the second sound (split distance over 0.05 sec.) over pulmonic area in 30 (69.7%) (Fig. 4). Group 2 consisted of 9 patients and showed similar incidence of gallop rhythm and split pulmonic second sound as group 1, but distinguished from group 1 in regard to the absence of presystolic gallop rhythm. In group 3, there were 13 patients,

Table I. Abnormalities in Heart Sounds

	Group 1 (43 cases)		Group 2 (9 cases)		Group 3 (13 cases)	
	Active	Inactive	Active	Inactive	Active	Inactive
Gallop rhythm	26 (60.4%)	0	5 (55.6%)	0	0	0
protodiastolic	16	0	2	0	0	0
presystolic	3	0	0	0	0	0
summation	5	0	1	0	0	0
quadruple	2	0	1	0	0	0
systolic	0	0	1	0	0	0
Abnormal splitting of second sound over pulmonic area	30 (69.7%)	3	6 (66.7%)	0	8 (61.5%)	2
With gallop	18	0	3		0	0

and split pulmonic second sound was the sole finding, showing the same incidence as in group 1 and 2. Among various types of gallop rhythm, protodiastolic gallop (Fig. 2) occurred most frequently, 18 out of 31 cases (58%), and presystolic gallop occurred only in group 1.

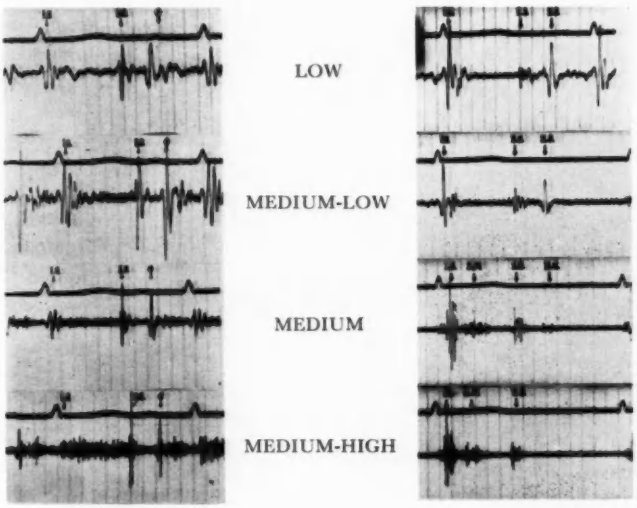

Fig. 2. Phonocardiogram at apex.

(a) A 12-year-old boy. Tracing was made at acute stage. High-pitched holosystolic murmur, loud 3rd sound (triple rhythm) and moderate diastolic murmur just followed after gallop sound.

(b) At convalescent stage. Disappearances of diastolic murmur, regress of 3rd sound and systolic murmur (only early and faint systolic murmur).

Electrocardiographically delayed a–v conduction was seen in 15 out of 26 cases with gallop rhythm in group 1 and 4 out of 5 cases in group 2. Increased QTc coincided with gallop rhythm less frequently, 10 in group 1 and 2 in group 2.

Moderate to marked enlargement of cardiac silhouette on X-ray examination was recognized in most cases with gallop rhythm. This condition was explained by increase in cardio-thoracic ratio and ranged from 0.50 to 0.78 with a mean of 0.58.

When rheumatic activity was subsided, these abnormalities of heart sounds disappeared in the majority of cases (Table I, Fig. 2.).

B. Heart Murmurs (Table II, Fig. 2, 5, 6)

Configuration and type of heart murmurs over the different areas were also influenced by the rheumatic activity. In Table II, changes in type

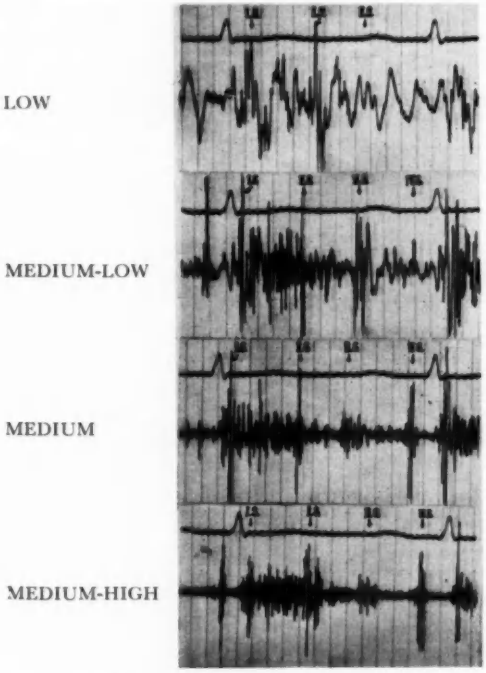

Fig. 3. Phonocardiogram at apex.

A girl aged 11. PCG shows high-pitched holosystolic murmur and quadruple rhythm.

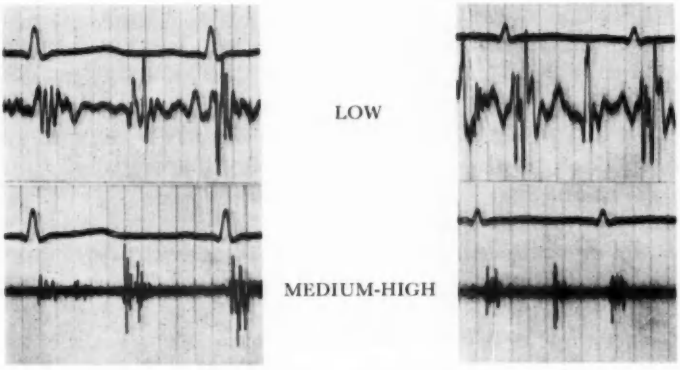

Fig. 4. Phonocardiogram over pulmonic area.

(a) In active phase. Distance of splitting 2nd sound is 0.05 sec.

(b) In inactive phase. Minimal splitting of 2nd sound.

Table II. Type and Configuration of the Murmurs over the Different Areas

	Group 1 (43 cases)		Group 2 (9 cases)	
	Active	Inactive	Active	Inactive
Apical systolic murmur	43	39	9	6
holosystolic, harsh	43	31	9	6
in decrescendo	22	17	3	2
in crescendo	9	7	2	2
in diamond shaped	12	8	4	2
early or mid-systolic	0	8	0	2
minimal or absent	0	4	0	1
Apical diastolic murmur	29	8	5	2
proto-diastolic	5	4	0	0
mid-diastolic	22	3	5	2
presystolic	2	1	0	0
Basal diastolic murmur	12	9	0	0

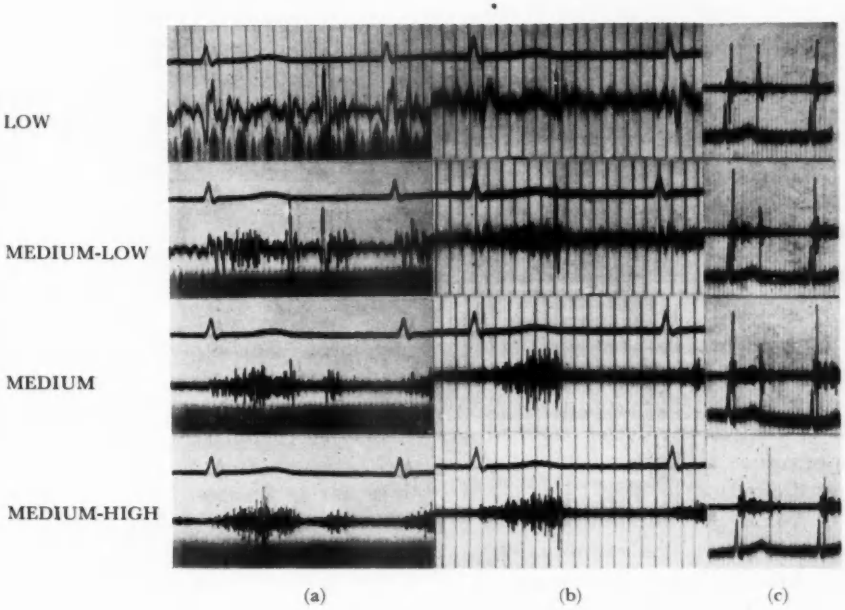

Fig. 5. Phonocardiogram at apex.

A girl aged 11. (a) 12 days after onset of illness. High-pitched diamond-shaped holosystolic murmur, loud 3rd sound and mid-diastolic murmur. (b) 2 months later. Loud 3rd sound and mid-diastolic murmur disappeared and systolic murmur altered its configuration to crescendo type. (c) 1 year later. Opening snap, a small vibration about 0.08 sec. after 2nd sound.

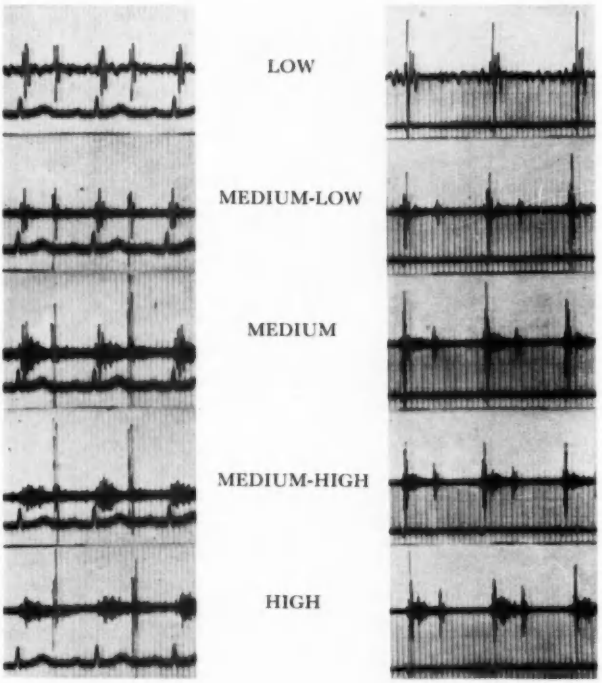

Fig. 6. Phonocardiogram over aortic area.
A boy, 12 years of age. (a) Diastolic murmur of grade 3 with relatively short duration in active phase. (b) 48 days later, activity subsided with simultaneous disappearance of diastolic murmur.

and configuration of the murmurs are presented. In both group 1 and 2 apical "holosystolic" murmurs have already been present in all instances at the first examination and its characteristics remained in about 74% and 67%, respectively, after the subsidence of the rheumatic activity. Disappearance of holosystolic murmur was observed in only 4 cases and transformation to early or mid-systolic murmur in 8 cases (Fig. 2).

Apical diastolic murmur was present in 29 of group 1 and in 5 of group 2 at the first examination and co-existence of apical systolic murmur was seen in 86% of both groups. By regress of rheumatic process, 24 cases of those with apical diastolic murmur have lost their characteristic murmur. Particularly, mid-diastolic murmur disappeared most frequently (22/27, 81%) (Fig. 2, 5).

Basal diastolic murmur was observed in only group 1, and it disappeared in 5 (Fig. 6) and appeared in 2 after subsidence of the activity.

Disappearance of significant murmurs was concomitant with decrease

in degree of the cardiac enlargement, cardio-thoracic ratio showed a marked diminution during this period.

II. Alteration of the apical E/M.

As previously reported,[3] mean value of this ratio in normal children and adolescents lies 103±6; in most cases with active rheumatic carditis the value exceeds this level and is altered by degree of the rheumatic activity (Fig. 7, 8)

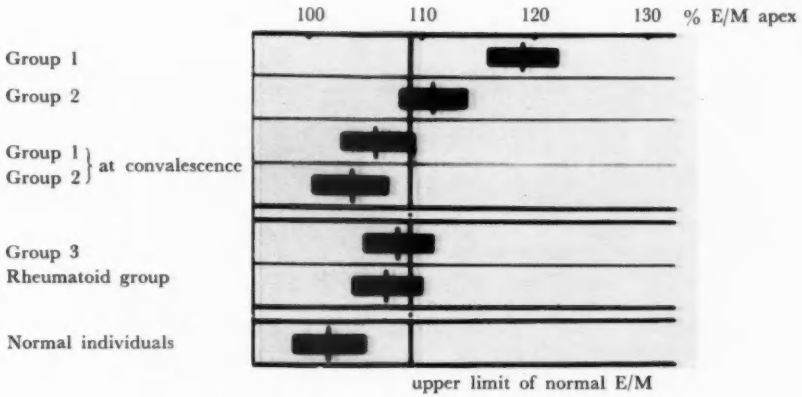

Fig. 7. Statistical distribution of apical E/M.

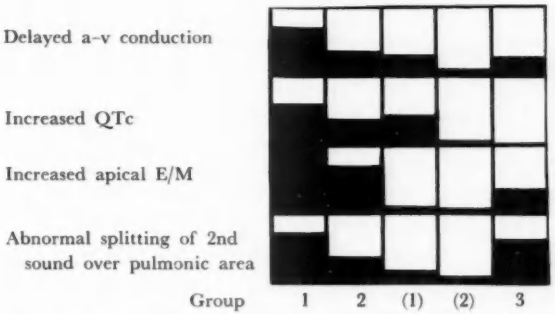

Fig. 8. Statistical distribution of electro- and phonocardiographic findings. Black column indicates the occurrence of each items. (1), (2) at convalescent phase of group 1 and 2 respectively.

A. Apical E/M and Electrocardiographic and Phonocardiographic Findings (Table III)

Either lengthening of the electrical systole and / or shortening of the mechanical systole appeared to produce an increased apical E/M. This relationship is represented in Table III. In group 1 lengthening of the

Table III. Factors in Increasing Value of Apical E/M

(A) Cases associated with prolonged QT-interval (24 cases).

	No. of patients	Q-I* > 0.06″		Q-I ≦ 0.06″		Total
		QT-QII** > 0	QT-QII ≦ 0	QT-QII > 0	QT-QII ≦ 0	
Group 1	43	8	4	6	1	19
Group 2	9	2	2	1	0	5
Group 3	12	0	0	0	0	0
Total		10	6	7	1	24

(B) Cases associated with normal QT-interval (31 cases).

Group 1		3	8	7	6	24
Group 2		1	1	1	1	4
Group 3		0	0	2	1	3
Total	65	4	9	10	8	31

Note:

* Q-I: Distance from the beginning of Q-wave on the electrocardiogram to that of the central phase of 1st sound on the phonocardiogram at apex.

** Q-II: Distance from the beginning of Q-wave on the electrocardiogram to that of 2nd sound on the phonocardiogram at apex.

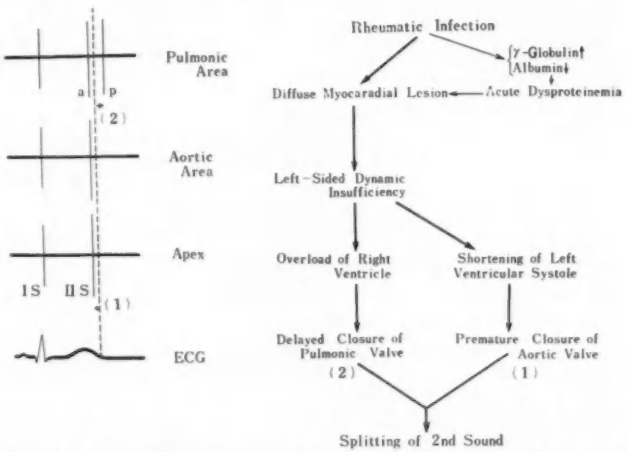

Fig. 9. Probable mechanism of the abnormal splitting of 2nd sound over pulmonic area.

Left: Attitude of 2nd sound over different areas. At apex, 2nd sound occurs before the completion of "repolarization" (dotted line) owing to mechanism (1). Over pulmonic area, "IIa" is coincident with 2nd sound at apex and aortic area, and "IIp" occurs fairly after the completion of repolarization owing to mechanism (2).

Right: Probable patho-physiological basis for occurrence of abnormal splitting of 2nd sound over pulmonic area.

electrical systole seemingly resulted in a more marked increase in apical E/M. But in other items of this table significant difference could not be found out.

B. Apical E/M and Splitting of 2nd Sound over the Pulmonic Area

In Fig. 9, the mode of splitting is presented. The second sound over pulmonic area in rheumatic fever became split as a result of shortening of the ventricular mechanical systole in the left sided heart producing premature closure of the aortic valve occurring during the end of systole and delay in the closure of the pulmonic valve in the right side of the heart (Fig. 10).

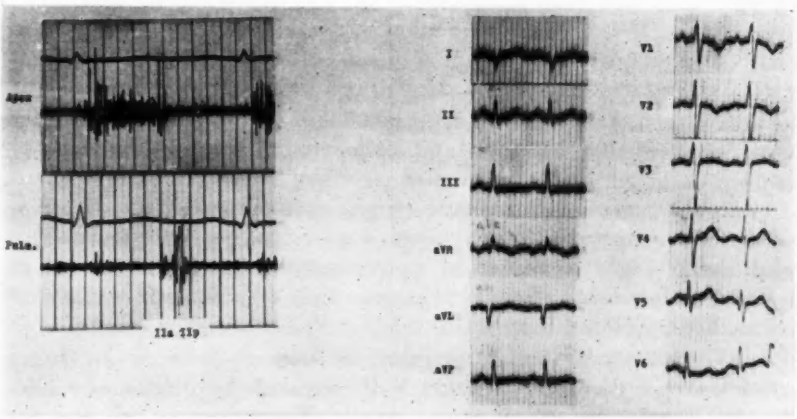

Fig. 10. Abnormal split of 2nd sound over pulmonic area.

Left: Phonocardiogram at apex and over pulmonic area. Distance between 1st and 2nd sound at apex equal to distance between 1st and "pulmonic component" of 2nd sound over pulmonic area. Apical E/M is 132%. QTc 0.432.

Right: Electrocardiogram shows slight ventricular hypertrophy.

Discussion

The most common and generally the earliest clinical signs of carditis in acute rheumatic fever are murmurs. In 1835, Bouillaud[2] described at first auscultatory signs of a case with acute rheumatic fever. Since about a century ago many reports on the characteristics of the auscultatory data obtained from cases with acute rheumatic fever have been published.

Graphic registration of murmurs due to acute "valvulitis" was first performed by Schwarzchild and Feltenstein[1] in 1935. Since then advantage of phonocardiographic method for diagnosis of carditis has been recognized.

In our series apical systolic murmur had already been present in all cases at the first examination and it had high-pitched and holosystolic

character. On the phonocardiogram, various types of configuration were observed as follows. Systolic murmur in decrescendo, which was characteristic of mitral regurgitation according to Luisada's description,[7] was found in about one half of them and persisted throughout the course. In remaining one half, there were crescendo and diamond-shaped murmurs. The latter murmurs were relatively inconstant, and became minimal or disappeared in 4 instances.

Dual theories concerning the pathogenesis of apical systolic murmur have been suggested in the past. One of the theories originates on the basis of dilatation of left ventricle and mitral valve ring or mitral incompetency.[4)-6),8)-10)] The other is based on improper closure of the mitral valve, which is due to inflammation and swelling of the mitral cusps.[11)] Luisada and Magri[12)] considered that (1) dilatation of mitral ring, (2) edema and infiltration of the papillary muscle, and (3) edema of mitral leaflet may be responsible for the production of this murmur. Zilli and Gamna[13)] have shown that apical systolic murmur was caused by the dilatation of mitral ring and stretching of papillary muscle in both early stage and established mitral lesion after disappearance of the activity. Bland and Jones[14)] have pointed out that the apical high-pitched systolic murmur with long duration might be caused by an organic deformity of the mitral cusp if it became detectable after the disappearance of rheumatic activity. We agree with the opinion proposed by Zilli and Gamna.[13)]

The course of apical diastolic murmur was very interesting. In acute phase it was present in 34 cases and disappeared in 24 in convalescent phase. Especially the mid-diastolic murmur disappeared most frequently and rapidly. This particularity was first described by Coombs[9)] and often entitled "Carey Coombs' Murmur". Bland and Jones[15)] described this apical mid-diastolic murmur, if its intensity was minimal, was generated by the dilatation of the ventricle due to carditis and disappeared after a short duration. However, grade 3 to 4 mid-diastolic murmur if accompanied by systolic murmur was indicative of the deformity of mitral cusp. Luisada and Perez Montes,[16)] Zilli and Gamna[13)] pointed out that the mid-diastolic and presystolic murmur might be caused by an acute rheumatic carditis and would probably be due to "relative" mitral or tricuspid stenosis (dilatation of either venticle). Another theory concerning the cause of the diastolic murmur was described by Besterman[17)] who states that a stiffened cusps and surface irregularities due to inflammatory process set up eddy current during rapid ventricular filling phase and cause the mitral diastolic murmur. Jones[14)] experienced a girl whose physical signs of carditis gradually disappeared after several years and died of an accident. The autopsy revealed no significant changes in her heart except "healed endocarditis." Garber[18)] reported the rheumatic heart disease without microscopic valvulitis and he postulated the cardiac murmurs (both systolic and

diastolic) were probably due to myocarditis.
According to Massel,[19] the early inflammatory process is potentially reversible and the late fibrotic changes are not reversible. These facts might be reflected upon phonocardiographic findings!

The present study indicates that a rapid decrease in the cardio-thoracic ratio and apical E/M were evidently concomitant with the disappearance of apical diastolic murmur. Especially, mid-diastolic murmur disappeared in 22 out of 27 (81.5%). Of course, there occurred actual stenosis of mitral orifice due to inflammatory process as mentioned by Besterman[17], but we are of the opinion that the myocardial factor may play an important role for the development of the murmur.

Basal diastolic murmur was already present in 12 cases at the first examination. Its development to typical murmur of the aortic regurgitation occurred fairly later. But every case had high-pitched character and in 6 its duration reached to mid- to end-diastole. Delayed appearance was observed in 2 cases during the period of inactive phase. In 5 cases this type of murmur disappeared when rheumatic activity subsided, with decrease in degree of cardiac enlargement. In these cases, enlargement of the heart might be responsible for generating murmur to some extent.

As previously reported, there occurred significant discrepancy between electrical and mechanical phenomenon in rheumatic heart. Lengthening of the duration of electrical systole in rheumatic fever was noticed by Drawe et al.[20] Taran and Szialgyi[21] advocated that lengthening of the electrical systole was parallel with intensity of the rheumatic process. But such interpretation caused some discussion by Pokress and Goldberger.[22] At any rate, diffuse myocardial lesion may cause the increased QT-interval.

As shown in Table III and Fig. 7 and 8, increased QTc was present in 24 (44%) out of 54 cases associated with increased apical E/M. Among these 24 cases, 14 showed premature occurrence of second sound on the PCG. In 14 of 30 cases which had no prolongation of QT-interval, premature occurrence of second sound was seen before the completion of the ventricular repolarization.

Thus in 28 out of 55 cases, apparently shortened duration of the mechanical systole was revealed.

In rheumatic carditis, inevitable myocardial damage occurs in left ventricle to some extent, and it may be promoted by coexisting acute dysproteinemia produced by an increase in γ-globulin and a decrease in albumin after rheumatic infection.[23],[24] Under these circumstances, left-sided dynamic insufficiency will become evident and as a consequence following 2 phenomena will occur: premature closure of aortic valve in left side and delayed closure of pulmonic valve in right side, the latter being introduced by the right ventricular overloading secondary to the left-sided dynamic insufficiency. This, in turn, produced splitting second sound over pulmonic area.

Summary

(1) Repeated phonocardiographic examinations are valuable for diagnosis, evaluation and the treatment of rheumatic fever.

(2) Early phonocardiographic changes characteristic for active carditis are as follows:

(a) High-pitched holosystolic murmur at the apex.

(b) Relatively short mid-diastolic murmur at the apex.

(c) Loud extra sound, especially 3rd sound. Frequent occurrence of gallop rhythm.

(d) Abnormal splitting of second sound over pulmonic area.

(3) Apical diastolic murmur is caused mainly by dilatation of the left ventricle with flabby myocardium and will disappear easily by treatment.

(4) Increasing value of apical E/M is proportional to the rheumatic process.

(5) In the mechanism of the genesis of split pulmonic second sound, premature closure of aortic valve due to shortened mechanical systole of the left ventricle plays a certain role.

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Experimental Studies on the Beriberi Heart

I. Cardiac Lesions in Thiamine Deficient Rats

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and Seizo YAMASHITA, M.D.

To elucidate the mechanism of the cardiac lesions due to thiamine deficiency, authors have been carrying on studies on the cardiac lesions in pure thiamine deficient rats.

In this paper, the general progress, electrocardiograms and histological findings observed on control normal rats and on thiamine deficient rats are reported.

IT is generally recognized that one of the main symptoms of beriberi is cardiovascular disturbance caused by thiamine deficiency. But the etiology—why the cardiac lesions occur owing to thiamine deficiency—is not well known.

On the other hand, up to date most clinical studies on "myocardosis", the concept introduced by pathologist, have been carried out in connection with disturbances of protein and electrolyte metabolism and not with disturbances of carbohydrate metabolism. Therefore, our opinion is that the myocardial lesion caused by the disturbances in carbohydrate metabolism (including the thiamine deficiency) is the problem that requires further study.

As such, to make clear the mechanism of beriberi heart, has an important significance not only in vitaminology, but in cardiology as well concerning the biological process and energy metabolism in cardiac muscles, myocardosis etc.

From these points of view, the authors have been studying on cardiac lesions in pure thiamine deficient rats. The following is the result of our studies on the electrocardiographic changes and on the histological findings observed at various stages of thiamine deficiency.

Methods

1) Feedings:

Young male rats were at first kept on normal diet. When their body weight became about 60 to 70 Gm., they were divided into 2 groups, one a control normal

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group and the other a thiamine deficient group. The diet and method of feeding are as given in Table I.

Table I. Composition of Diet

Basic diet		*Salt mixture		B_2 group	
Casein	72	NaCl	20.2	B_2	4.0 mg
Starch	272	$MgSO_4 \cdot 7H_2O$	63.5	B_6	5.0
*Salt mixture	16	K_2HPO_4	111.5	Nicotinic acid	20.0
Soy-bean oil	24	Ca-lactate	28.7	Ca-Pantothenate	20.0
Cod liver oil	9.6	$Na_2HPO_4 \cdot 12H_2O$	52.6	Choline-HCl	90.0
Water	480	$Ca_2H_2(PO_4)_2 \cdot H_2O$	111.6	Inositol	18.0
These are mixed in the above proportion, cooked and made into cakes.		Fe-Citrate	13.8	B_{12}	2.4 γ
				DL-Methionine	24.0 mg
				The above are made into 10 ml. of liquid.	

Administration
- Thiamine deficient group: The basic diet is given more than the rats can eat. B_2 group (0.1 ml.) is given orally every day.
- Control normal group: The basic diet is given more than the rats can eat. B_1 (40 γ) and B_2 group (0.1 ml.) are given orally every day.

2) Electrocardiographic examination:

Unanesthetized rat was placed on its abdomen on a board to which its feet were tied, and electrocardiographic recordings were made at intervals of from a few days to one week throughout the study. Electrodes were dipped in electrode paste and these were taped to the feet soles of the rat with adhesive plaster. The face of the rat was covered with gauze mask to keep them still. Electrocardiographic examination was started several minutes after the rat became quiet and standard limb lead and unipolar limb lead were recorded. We used the same standardization as men's electrocardiography (1 mV.: 1 cm.). The room temperature was kept at about 20-25°C at all times during the examination.

3) Histological examination:

The rat was anatomized after it was slightly anesthetized with ether and then the heart was quickly taken out. After weighing with torsion balance, the heart was fixed and stained with Sudan III (S III), Hematoxyline-Eosin (H. E) and PAS.

Results

1. General Observations.

A) Control normal group:

Appetite has always been good and daily food intake was about 20–30 Gm. The body weight increased from about 50 Gm. to about 150 Gm. in about 4 weeks, showing a daily increase in weight from several to 10 Gm.

(Fig. 1). During this time vitality was good and stools were hard and brown. No abnormality was seen in all examinations.

B) Thiamine deficient group:

In the first week of thiamine deficiency, growth, appetite, vitality and stools of this group were the same as those of the normal group. From the middle of the second week, appetite decreased gradually to about 15–20 Gm. a day, and the growth stopped, but vitality and stools were still good. In the third week the appetite decreased to about 10–15 Gm. a day, a decrease of about one-half as when in normal state, and the weight loss appeared clearly. But in general there was no change in the vitality and quality of the stools. In the fourth week, appetite decreased greatly and the daily food intake became only about 10 Gm. The body weight decreased markedly and showed a daily average loss of several grams. Most rats lost their vitality and revealed paralytic symptoms (in walking) and got diarrheas. Some rats died at the end of this week. In the fifth week the rats lost their appetite almost completely and daily food intake was only about 5 Gm. The body weight decreased extremely and became

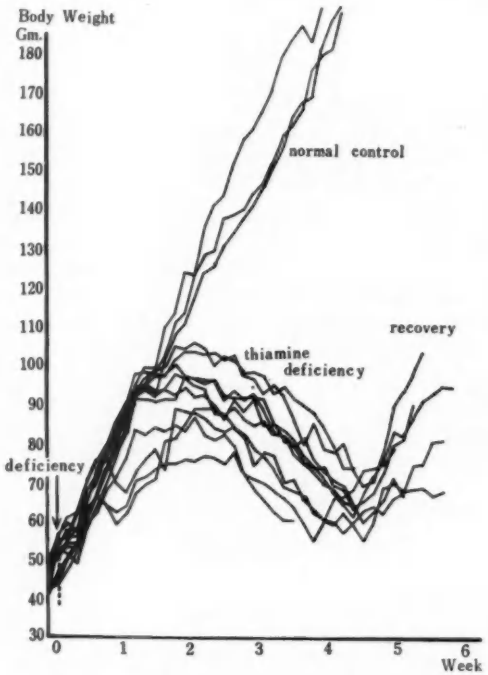

Fig. 1. The progress of body weight of control normal rats and thiamine deficient rats.

similar to that at the beginning of the thiamine deficient stage. Marked neuroparalytic symptoms and ataxia were observed during this period. All the rats became enervated and had stinking black-brown diarrhea. Most of the rats died during this week (Fig. 1).

C) Group recovered from thiamine deficiency;

At the last stage of thiamine deficiency, oral administration of thiamine in daily doses of 5 μg was administered, and on the following day, this brought about an increase in appetite, vitality and body weight (Fig. 1). At the same time, within several days, paralytic symptoms and diarrhea were cured. Thereafter the general progress of these rats was similar to that of the normal group. However, extremely enervated rats died on the next day in spite of thiamine administration.

2. Electrocardiograms (ECG).

A) Control normal group:

Electrocardiograms were taken on 144 normal rats. They were divided into 5 groups by body weight (Table II). An example of a normal electrocardiogram is shown in Fig. 2.

Table II. Electrocardiographic Findings of Control Normal Rats

Body weight Gm. (average)	Cases	Heart rate (average)	Electrical axis			T maximum average valuemV.	Remarks
			Right	Left	Normal		
49.5—100 (69.9)	60	574	5 8.3%	16 26.7%	39 65%	0.22	one case of ST 0.12 mV.
100.5—150 (131.5)	44	545	0	26 59.1%	18 40.9%	0.20	one case of ST 0.11 mV.
150.5—200 (162.0)	14	535	0	7 50%	7 50%	0.20	
200.5—250 (221.3)	9	514	0	7 44.4%	5 55.6%	0.17	
250.5—361 (283.5)	17	513	0	8 47.1%	9 52.9%	0.17	one case of R 0.1 mV.
Total	144	562	5 3.4%	61 42.4%	78 54.2%		In all cases; T_1: flat ST: within 0.1 mV. QRS: within 0.02 sec. PQ: about 0.05 sec. $R_{max.}$ value: 0.2~0.6 mV.

Heart rate: The heart rate was between 470–642/min. and showed negative correlation with body weight (Fig. 3).

Electrical axis: Right axis deviation was seen only in 5 cases of young

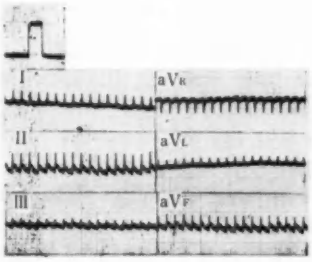

Fig. 2. Electrocardiogram of a normal rat (171 Gm.), heart rate 533.

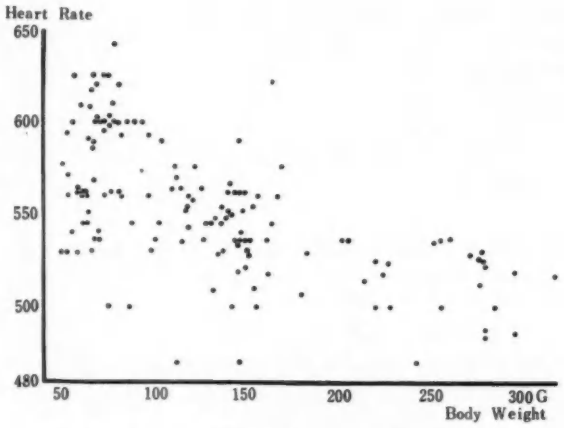

Fig. 3. Heart rate and body weight of normal rats.

rats with body weight under 100 Gm. and electrical axes were, for the most parts, normal axis and left axis deviation. In all cases, normal axis was more frequently seen than left axis.

T-wave: T_I was flat and $T_{II,III}$ were upright with an average main deflections of 0.17–0.22 mV.

ST-segment: It varied within 0.1 mV from the base line.

R-wave: The main deflection varied between 0.2–0.6 mV. The rats with body weight over 250 Gm. seemed to have low R wave.

PQ-interval: It was about 0.05 second.

QRS-duration: It was within 0.02 second.

B) Thiamine deficient group:

Electrocardiograms were taken before and after the start of thiamine deficiency until the last stage, and all cases were 221. The summary is shown in Table III.

Heart rate: The heart rate fell gradually during the progress of thiamine deficiency and marked bradycardia appeared in the last stage.

Table III. Electrocardiographic Findings of Thiamine Deficient Rats

Week of thiamine deficiency		Cases	Heart rate average	Cases of arrhythmia	Electrical axis			S T		T	
					Right	Left	Normal	Elevation	Depression	Elevation	Depression
1		20	550	0	2 10%	12 60%	6 30%				
2		42	523	0	10 23.8%	9 21.4%	23 54.8%	8 19%	3 7.1%	9 21.4%	
3		59	446	1 1.7%	23 39%	13 22%	23 39%	11 18.6%	7 11.9%	11 18.6%	23 39%
	moribund condition	4	225	2 50%	1 25%	1 25%	2 50%	2 50%	1 25%	1 25%	1 25%
	total	63		3 4.8%	24 38.1%	14 22.2%	25 39.7%	13 20.6%	8 12.7%	12 19%	24 38.1%
4		45	410	8 17.8%	21 46.7%	2 4.4%	22 48.9%	21 46.7%	6 13.3%	13 28.9%	26 57.8%
	moribund condition	14	208	7 50%	4 28.6%	2 14.3%	8 57.1%	8 57.1%		8 57.1%	4 28.6%
	total	59		15 25.4%	25 42.4%	4 6.8%	30 50.8%	29 49.2%	6 10.2%	21 35.6%	30 50.8%
5		32	331	18 56.2%	11 34.4%	3 9.4%	18 56.2%	11 34.4%	5 15.6%	11 34.4%	11 46.9%
	moribund condition	5	166	3 60%	1 20%	3 60%	1 20%	2 40%	1 20%	1 20%	3 60%
	total	37		21 56.7%	21 32.4%	6 16.2%	19 51.4%	13 35.1%	6 16.2%	12 32.4%	18 48.7%
Total		221		39 17.6%	73 33%	45 20.4%	103 46.6%	63 28.5%	23 10.4%	54 24.4%	72 32.5%

In the cases where heart rate fell below 200/min. the rats were in dying conditions (Fig. 4).

Arrhythmia: Arrhythmia appeared from the middle of the third week and it increased during the progress of deficiency. The total cases of arrhythmia were 39 and these were; sinus arrhythmia (18), a–v block (10), interpolated nodal rhythm (9), and premature beat (supraventricular 1, ventricular 1).

Electrical axis: Right axis deviation was seen in 10% of cases in the first week and it markedly increased during the progress of deficiency. On the contrary, left axis deviation was seen in 60% in the first week, but markedly decreased during the progress of deficiency. Normal axis showed a slight decrease compared with the control normal group. These comparisons are shown in Table IV.

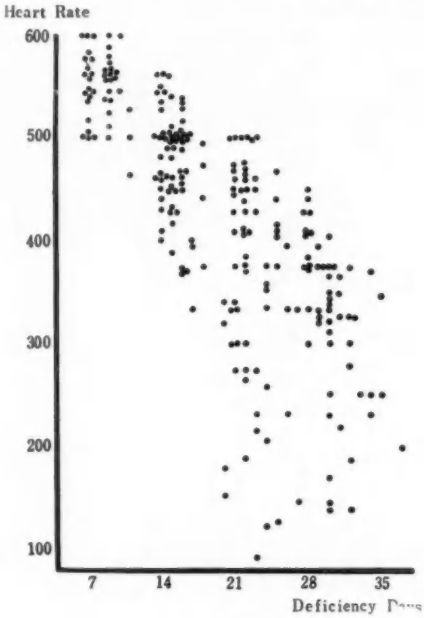

Fig. 4. Heart rate of thiamine deficient rats.

Table IV. Electrical Axis of Normal and Thiamine Deficient Rats

Condition	Cases	Right axis	Left axis	Normal axis
Normal 49.5~150 Gm.	104	5 (4.8%)	42 (40.4%)	57 (54.8%)
Thiamine deficiency 1~5½ weeks	221	73 (33.0%)	45 (20.4%)	103 (46.6%)

ST-segment: Elevation or depression (over 0.1 mV.) appeared from the second week and increased during the progress of deficiency. Altogether there were 63 cases (28.5%) of ST elevation and 23 cases (10.4%) of depression.

T-wave: From the second week, elevation, and from the third week depression of T-wave appeared and both increased during the progress of deficiency. Altogether there were 54 cases (24.4%) of elevation and 72 cases (32.5%) of depression.

PQ-interval: Usually no change was observed except in the cases of a–v block.

QRS-duration: Generally, no change was found except in moribund cases.

R-wave: In many cases high R-wave was observed.

Examples of these changes are represented in Fig. 5–17.

Fig. 5: ST elevation, 6: ST depression, 7: ST elevation and depression, 8: T elevation, 9: T flat, 10: T negative, 11: incomplete a–v block, 12: supra-ventricular premature beat, 13: interpolated nodal rhythm, 14: ventricular premature beat, 15: prolongation of PQ-interval, 16: a–v block and interpolated nodal rhythm, and 17: agonal case.

C) Effect of thiamine administration on thiamine deficient electrocardiogram:

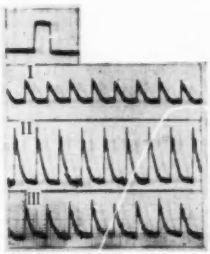

Fig. 5. 22 days of thiamine deficiency, 64 Gm., rate 187.

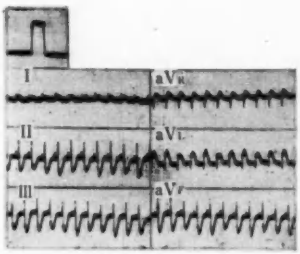

Fig. 6. 23 days of thiamine deficiency, 71.5 Gm., rate 346–333.

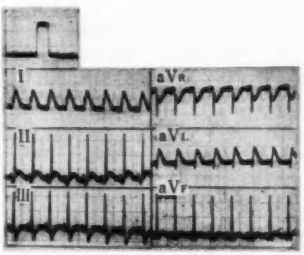

Fig. 7. 33 dyas of thiamine deficiency, 69 Gm., rate 250–231.

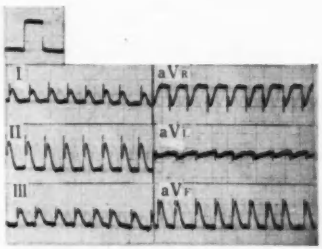

Fig. 8. 30 days of thiamine deficiency, 74.5 Gm., rate 250–200.

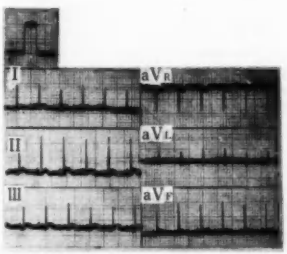

Fig. 9. 37 days of thiamine deficiency, 76.5 Gm., rate 197.

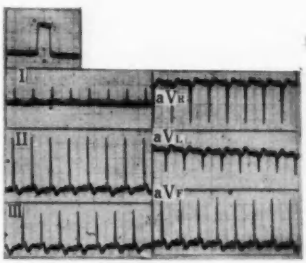

Fig. 10. 26 days of thiamine deficiency, 71 Gm., rate 231.

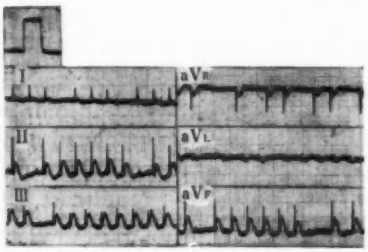

Fig. 11. 23 days of thiamine deficiency, 74 Gm., rate 273–100.

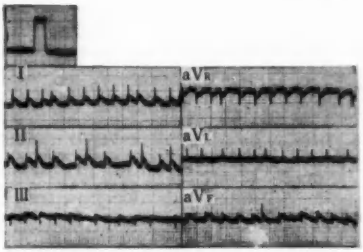

Fig. 12. 30 days of thiamine deficiency, 89 Gm., rate 484–172.

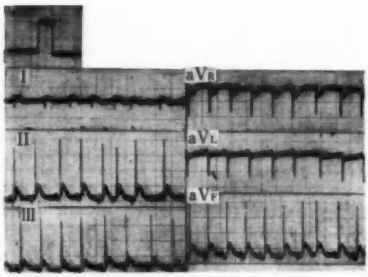

Fig. 13. 32 days of thiamine deficiency, 69 Gm., rate 326–150.

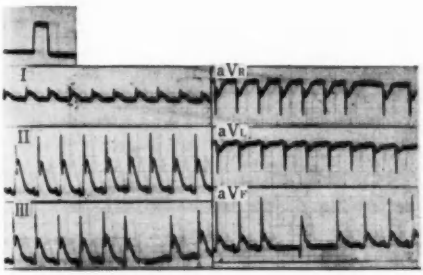

Fig. 14. 24 days of thiamine deficiency, 73 Gm., rate 204–100.

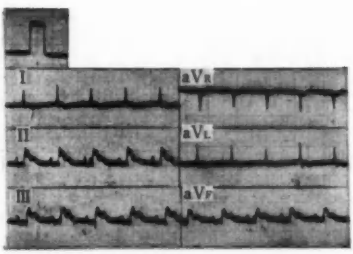

Fig. 15. 27 days of thiamine deficiency, 89 Gm., rate 128.

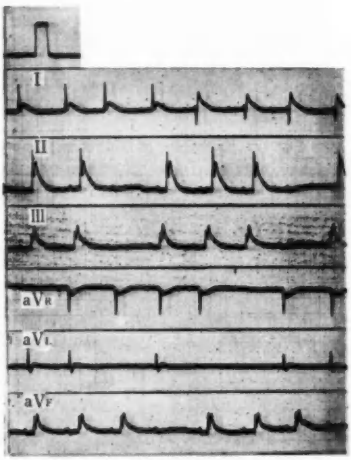

Fig. 16. 24 days of thiamine deficiency, 66.5 Gm., rate 120–37.

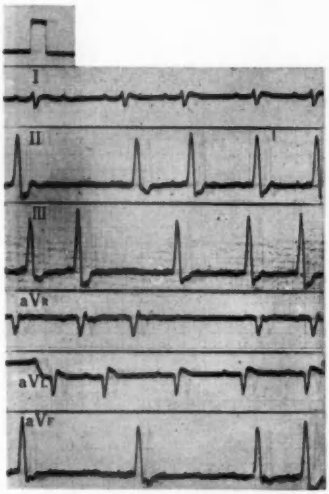

Fig. 17. 27 days of thiamine deficiency, 89 Gm., rate 96–39.

After intramuscular injection (on the right foreleg) of 1 mg. of thiamine, electrocardiograms were taken at intervals of 15–30–60 minutes for about 4 hours.

a) In the cases of from the second to the fourth week of deficiency: 15–30 minutes after the injection, such changes as bradycardia, right axis deviation, T-wave changes, ST changes and arrhythmia began to improve and more marked improvement was observed as time progressed.

Fig. 18–22 represent one case of this group. Fig. 18 is a case of the 23rd day of deficiency showing marked arrhythmia, bradycardia, and high T-waves. Thirty minutes after the injection (Fig. 19), arrhythmia and bradycardia began to improve, and 60 minutes later (Fig. 20), ar-

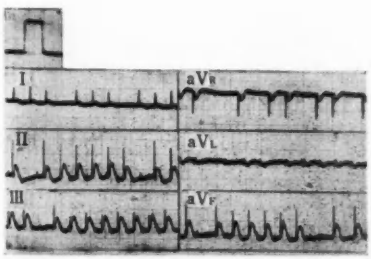

Fig. 18. Before thiamine injection, A case of the 23rd day of thiamine deficiency, 74 Gm., rate 273–100.

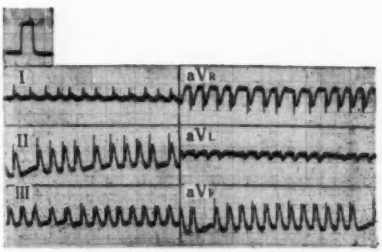

Fig. 19. 30 minutes after injection, rate 357–187.

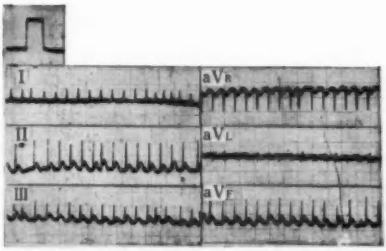

Fig. 20. 60 minutes after injection, rate 391–231.

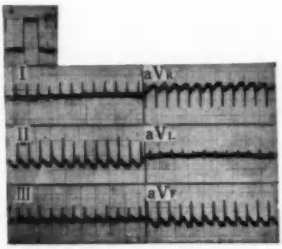

Fig. 21. 90 minutes after injection, rate 391.

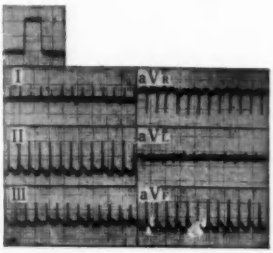

Fig. 22. Four hours after injection, rate 428.

rhythmia, bradycardia and high T-waves showed marked improvement. Ninety minutes later (Fig. 21) arrhythmia and high T-waves disappeared and heart rate showed much increase, and these were the same 4 hours later (Fig. 22).

b) In the cases of after the end of the fourth week of thiamine deficiency: After the injection some improvements were seen for a while, but in general, the improvements were not so marked as in the cases of those before the fourth week as mentioned in above. Furthermore almost no effect was observed in moribund cases.

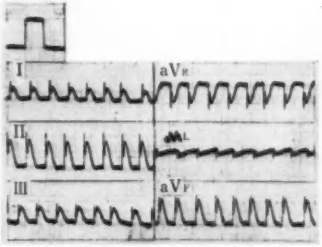

Fig. 23. Before thiamine injection, A case of the 30th day of thiamine deficiency, 74.5 Gm., rate 250–200.

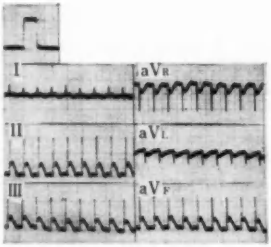

Fig. 24. One hour after injection, rate 300.

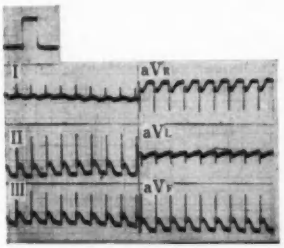

Fig. 25. Two hours after injection, rate 346.

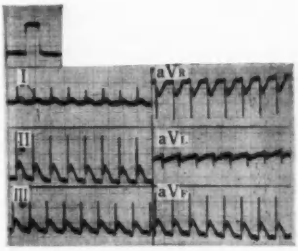

Fig. 26. Four hours after injection, rate 250.

Fig. 23 represents a case of the 30th day of deficiency showing ST elevation, high T-wave, marked bradycardia, and arrhythmia. Thirty minutes after the injection, bradycardia and arrhythmia began to improve. Sixty minutes later (Fig. 24), arrhythmia disappeared and ST elevation, high T-wave, and bradycardia markedly improved. But, the maximum improvement was 2 hours after the injection (Fig. 25). Conditions took a bad turn from 3 to 4 hours (Fig. 26) after the injection (long time fixation had considerably influenced this change for the worse). But, marked improvement was observed on the following day.

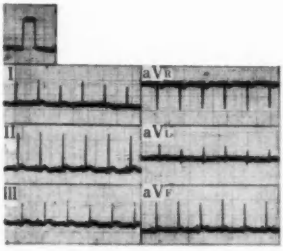

Fig. 27. Before thiamine injection, A case of the 37th day of thiamine deficiency, 76.5 Gm., rate 197.

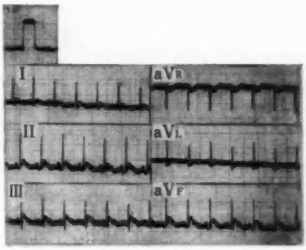

Fig. 28. One hour after injection, rate 205.

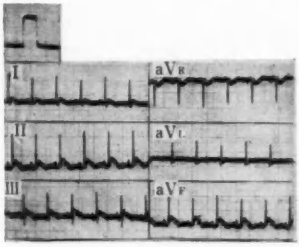

Fig. 29. Two hours after injection, rate 177.

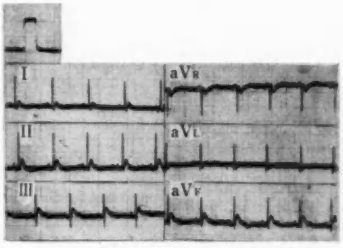

Fig. 30. Four hours after injection, rate 129.

Fig. 27 represents a case of the 37th day of deficiency in which the rat was in dying condition and showed marked bradycardia and flat T-waves. After the injection of thiamine (Fig. 27–30), no improvement was seen.

3. Histological Findings.

A) Heart weight (per 100 Gm. of body weight):

Table V. Average Heart Weight (per 100 Gm. of body weight)

Condition		Cases	Heart weight mg.
Normal rats		4	409.0
Thiamine deficient rats	1st week	2	405.5
	2nd 〃	3	454.7
	3rd 〃	4	438.0
	4th 〃	8	554.0
	5th 〃	6	575.7

The average heart weight is shown in Table V. In the control normal group, it was 409.0 mg. In thiamine deficient group, the weight increased from the second week, and showed a marked increase, such as 554.0 mg. (in the fourth week), 575.7 mg. (in the fifth week). All cases are represented in Fig. 31. The mark ⊙ shows paralytic case with no increase in heart weight,

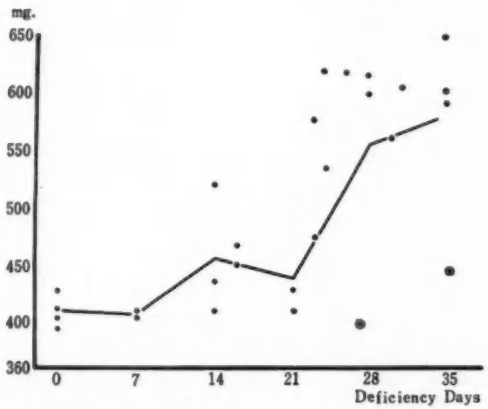

Fig. 31. Heart weight (per 100 Gm. of body weight).

but even including cases with this mark, a great increase in mean value was observed. These cases of increase in heart weight showed a vertical position of the heart in the thorax and a bag shape heart caused by right heart enlargement. One case is shown in Fig. 32. Though thiamine

deficient heart seems smaller than control normal heart, it is larger than the latter in proportion to the body weight.

Fig. 32. Heart of the rat.
Left: from a case of the 41st day of deficiency
Right: from a normal case

B) Myocardial findings:

No change was found in the control normal group. In the thiamine deficient group, fat granule in myofibrils began to increase from the 16th day and a high-degree of increase was found as the deficiency progressed. But there was no change in quantity of glycogen. The degeneration began to appear from the 30th day of deficiency and separation of myocardial fibers and granulation of cell plasma were found in one case. Vacuolar degeneration and karyopyknosis were observed in a case of the 41st day of deficiency.

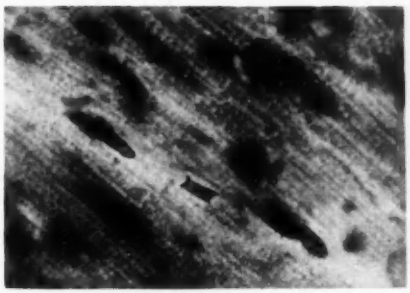

Fig. 33. Myocardium of the normal rat (SIII).

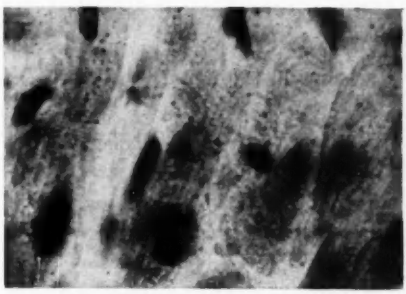

Fig. 34. Increase of fat granule in myofibrils on a case of the 30th day of deficiency (SIII).

Table VI. Myocardial Findings

Condition		S III	H·E	PAS
		Fat granule	Degeneration	Glycogen
Normal		±	−	+
		±	−	+
Thiamine deficiency	16th day	±	−	+
		+	−	+
	23rd day	++	−	+
		++	−	+
	30th day	+++	granulation of cell plasma and separation of myocardial fibers	+
		+++	−	+
	41st day	+++	vacuolar degeneration karyopyknosis	
Recovery from thiamine deficiency	4th day *(31 days)	±	necrosis +	
	5th day (31 days)	−	necrosis + vacuolar degeneration	
	6th day (31 days)	−	vacuolar degeneration	
	8th day (26 days)	−	?	
	10th day (30 days)	−	−	
	11th day (28 days)	−	fibrous focus (healing traces of necrosis)	
	11th day (28 days)	−	fibrous focus (healing traces of necrosis)	

Note: * The number of days in the parentheses show the deficiency days.

In the recovery group from thiamine deficiency (recovered from the last stage of deficiency by oral administration of thiamine in a daily dose of 5 μg.), fat granule disappeared, while necrosis and vacuolar degeneration were found for about a week. After 10 days, there were cases where no abnormalities were found and cases where mere healing traces of necrosis were found. Summary is shown in Table VI.

Some microphotographs are represented in Fig. 33–38. Fig. 33: normal heart (S III), Fig. 34: increasing fat granule and disappearance of horizontal stripes in a case of the 30th day of thiamine deficiency, Fig. 35: normal heart (H.E.), Fig. 36: marked vacuolar degeneration and karyopyk-

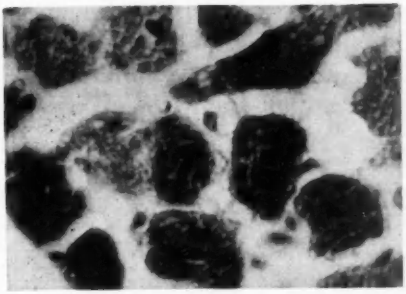

Fig. 35. Myocardium of the normal rat (H·E).

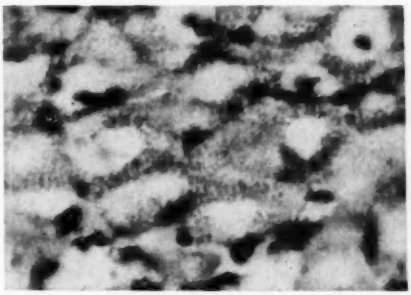

Fig. 36. Vacuolar degeneration and karyopyknosis in a case of the 41st day of deficiency (H·E).

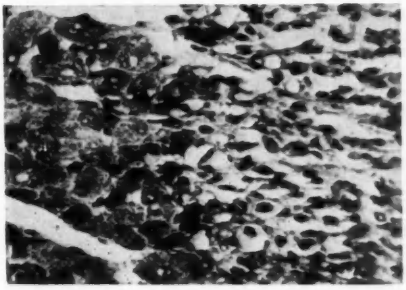

Fig. 37. Typical necrosis in a case of fourth day of recovery from deficiency (thiamine (5 γ) was given orally every day from the 31st day of deficiency).

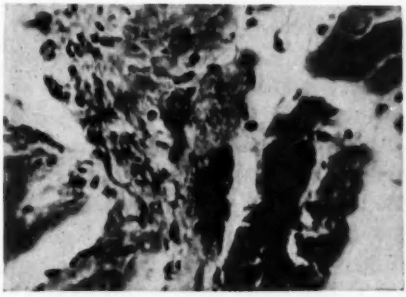

Fig. 38. Fibrous focus (healing traces of necrosis) in a case of the 11th day of recovery from deficiency (thiamine (5 γ) was given orally every day from the 28th day of deficiency).

nosis in a case of the 41st day of deficiency, Fig. 37: typical necrosis in a case of 4th day of recovery, and Fig. 38: healing fibrous focus of necrosis in a case of 11th day of recovery.

Discussion

1) General observation and the feeding:

Up to now there have been many reports[1] concerning investigations on thiamine deficiency. However, together with the recent progress on the studies on vitamins, it has been found out that most experiments of the so-called thiamine deficiency were B complex as well as nutrition deficiencies in the diet.[2] It is a matter of course then that such reports require reinvestigation.

Moreover, the results of the thiamine deficiency experiments have not

always been the same but in a great many instances have rather contradicted each other. Main causes of these differences were in the diet and the feeding method. Therefore, in order to ascertain first of all a full diet and feeding method, our investigation was carried out before the experiment on the general conditions of the rats.

In our investigation, the normal control group showed normal growth, good general condition, and normal findings in all examinations, and we were able to confirm that the diet was not nutritionally deficient. Moreover, on the thiamine deficiency group, a definite progress of deficiency symptom was observed and we were able to confirm that, by quick recovery through thiamine administration, the present diet was complete for the thiamine deficiency food.

As regards deficiency, from about the fourth week, appearance of paralytic symptoms and diarrhea were noticed besides decrease in appetite and body weight and these could be quickly cured by the administration of thiamine. These are similar to those of human beriberi. On the other hand, the fact that there were no symptoms of edema or ascites but on the contrary the whole body dried into a dehydrated condition, is in sharp contrast to the edema which is often seen in human beriberi. We think this is of interest from the point of etiology of beriberi edema.

2) Method of electrocardiographic examination:

In the electrocardiographic examination of unanesthetized animals, the difficulty everyone encounters is to keep them in a quiet state. As regards the examination of rats especially, the most important thing is to keep them in a quiet state, and this is also the most difficult problem. Accordingly, heretofore such fixation method as abdomen fixation or lay on back fixation have been used and as well as various electrodes, such as electrode of needle or copper wire.

In the old method, as there were unsatisfactory points in eliminating electrical disturbances and in keeping the rats quiet, we used the method mentioned before. Our method completely eliminated electrical disturbances and it was possible to keep rats in a quiet state during long hours of examination.

3) Electrocardiograms of normal rats:

In the recent description of Lepeschkin[3] on the heart rate, there was a big gap of 330 to 600 (average 490), T-waves were upright in all leads and the electrical axis in heavy body group showed an 18% right axis deviation. These are quite different from our findings. Judging from the heart rate alone, it is presumed that there was a defect probably in the normal diet or feeding method.

In our cases the heart rate was 470 to 642 (average 562). It showed an almost negative correlation with the body weight and the young rats had tachycardia. Moreover, the right axis deviation was observed in only

5 cases under 100 Gm. of body weight, and all cases above 100 Gm. were normal axis and left axis deviation. These correspond to the findings in men that infants have tachycardia and more marked right axis deviation and that as they grow the heart rate decreases and the right axis deviation also decreases. As the heart rate and electrical axis are related with the body weight in such way, even in the electrocardiograms of normal rats, we consider that a clear statement of body weight is necessary. Between Lepeschkin's description and our findings, there was a slight difference in values such as PQ, QRS, ST, T and R-wave. But, these values had no connections with body weight and these were almost constant and in this respect agree with our finding.

4) Electrocardiograms of thiamine deficient rats:

The electrocardiographic changes of experimental thiamine deficiency on pigeons were first reported in 1934 by Méhes and Péter[4], and thereafter there have been many reports on rats,[5] dogs[6],[7] and others. But, even in these the findings have not always been the same. There are some who stated that there was a specific changes in electrocardiogram, some who reported that there was no change[8]-[10] and some who said that the electrocardiographic changes seen in thiamine deficiency experiments were on account of starvation accompanied by deficiency,[11]-[13] and they had not come to any definite conclusion. Here, the differences in the thiamine deficient diet and deficient days, the differences in standard for judging deficiency symptoms and extent of starvation can be given as the biggest factor of such differences. Also, in previous studies, while mentioning thiamine deficient experiments there were a few that investigated the deficiency progress and while discussing effect of starvation there were none who carried out close investigations of control underfed method. Furthermore, unlike men, the fact that it is difficult to carry on electrocardiographic examination on animals under a constant quiet state can be considered as one of the reasons of confusion.

As shown above that "the electrocardiographic changes of thimaine deficiency is non-specific"[14]-[16] has been, up to now, the opinion of most investigators.

As such, we investigated first of all the problem of diet as well as the electrocardiogram of the normal control group and then examined the electrocardiogram on the thiamine deficient stage in 221 cases. Up to now, because there was no constant thiamine deficiency stage owing to defects of thiamine deficient diet, there had not been enough close investigation on the progress and most were researches on last stage of thiamine deficiency. Considering the fact that these had been one of the causes of dispute, the study of the progress of thiamine deficient electrocardiogram has a very important significance. According to our cases, except in the hot July and August, a constant deficient progress was observed.

As regards electrocardiograms on thiamine deficiency animals, as there are many contradictory reports as shown above, we refer to cases we consider pertinent.

Bradycardia: Although it has long been known that bradycardia is caused by thiamine deficiency,[9] according to our 221 cases there is a complete negative correlation between the heart rate and the number of days of thiamine deficiency. At the fourth and fifth week of deficiency the heart rate reached about 300 and at about 200 the rats showed a moribund condition (a report on the mechanism of this bradycardia will follow later).

Arrhythmia: Heretofore there have been reports on block[4] and premature beat,[7),15),20),21] but according to our studies, arrhythmia appeared in the later part of the third week, increased in the fourth and fifth week, and was noticed in 17.6% of all cases. That it was confirmed in the sinus arrhythmia and the interpolated nodal rhythm besides the a-v block and the premature beat, is a finding that is worth noting.

PQ-interval: There is an old report[4] of a slight prolongation of PQ-interval, but it is generally believed that there occurs no change.[5),22] In our cases also, no change other than in a-v block was noticed.

QRS-duration: It is generally accepted that there is no prolongation[5] of QRS-duration and our findings agree with this.

QT-interval: It is generally said that prolongation occurs in QT,[15),25),27),28] and in our cases also prolongation was observed. A discussion on this will follow in a later report.

Electrical axis: Up to now we have not seen any reports concerning the electrical axis. In our study, together with the deficiency progress there was an increase of right axis. The decrease in the left axis was very noticeable and electrocardiographically a right heart enlargement could be surmised.

ST-segment: There are few reports on this and these few reports mentioned the depression[4),5] or the elevation[7] only. In our cases elevation or depression of ST-segment appeared after the second week. Together with the deficiency progress, abnormal cases increased and 28.5% ST elevation and 10.4% depression were noticed in all cases. We believe these have an important significance. A discussion on this will follow in a later report.

T-wave: There are many reports on this. Although it is said that elevation,[7),22] depression and inversion,[4),15),24),27),28] or both occur,[5),25] there are more reports on depression of the T-wave. In our cases, also a 24.4% elevation and a 32.5% depression were noticed in all cases. A discussion on this significance also will follow in a later report.

Just before death, extreme bradycardia, a–v block and ventricular automatism were noticed but these are considered as a phenomenon of moribund state and bear no special significance.

Next, as to electrocardiographic changes in beriberi heart disease the following are given up to now[14)-28)]; T abnormality (flat, bi-phasic, negative), slight change of QRS as well as low voltage, QT prolongation, premature beat, sinus tachycardia and increase of right ventricular strain. However these findings are not always observable and depending on the condition of the patient, there are many in whom no changes whatever are observed. Accordingly, in the western countries, as a diagnostic standard of beriberi heart, the Blaukenhorn standard[16)] is widely used. The standard is composed of the following eight items:

1) Enlarged heart with normal rhythm, 2) Dependent edema, 3) Elevated venous pressure, 4) Peripheral neuritis or pellagra, 5) Non-specific changes in electrocardiogram, 6) No other cause evident, 7) Gross deficiency of diet for 3 months or more, 8) Improvement and reduction of heart size after specific treatment, or autopsy findings consistent with beriberi. Here, the beriberi electrocardiographic findings are accepted as non-specific.

5) Electrocardiographic change at the time of thiamine injection:

Long ago Weiss[5)] noticed that vitamin B_1 injection in B_1 deficient rats and Swank in pigeons[29)] and dogs[7)] (in reality vitamin B group deficiency) improve the bradycardia as well as T-wave changes in a few hours to a few days. However, as both have limited the period of experiments (Weiss to about the fourth or fifth week of deficiency period when the heart rate become 300 to 350 and Swank to about the fourth week of deficiency period four or five days before the appearance of marked cardiac lesion) they had not come to a definite conclusion.

We studied the effect of thiamine injections every week in thiamine deficient rat groups one after another. While at the second to fourth week of deficiency, bradycardia, a–v block, right axis deviation, ST changes and T changes became normalized within one to a few hours after the injection, after the end of the fourth week the effect of thiamine injection was not so noticeable in a few hours but was very noticeable on the following day. And in 7 to 10 days a complete normalization of electrocardiographic changes occurred. From these results we were able to find out that the electrocardiographic changes in thiamine deficiency were mainly functional before the fourth week, and rather organic after fifth week. At the same time this makes us surmise that the marked electrocardiographic changes of arrhythmia, ST and T abnormality observed before the fourth week of deficiency were caused by biochemical disturbances. A report will follow later as to what kind of chemical changes played a principal role.

6) As mentioned, concerning rats with pure thiamine deficiency, it was confirmed that definite changes appeared on electrocardiogram together with the progress of the deficiency and that they returned quickly to normalcy by administration of thiamine. We think this has an important

significance in order to deny the previous findings that no electrocardiographic changes were observed in thiamine deficiency. Moreover owing to the fact that all kinds of electrocardiographic changes could be created through deficiency of thiamine alone, it can be considered that hereafter this can be utilized as an experimental means in analyzing abnormal electrocardiograms. Concerning the mechanism of these thiamine deficient electrocardiographic changes, a report will follow later.

7) Histological findings of the heart:

As regards the histological findings on beriberi heart, there have been many publications besides the reports by Wenkebach[15] and Shimazono.[30] Cardiac enlargement especially the right heart, weight increase, myocardial cloudy swellings, hyaline degeneration and fatty degeneration have been reported. On the other hand, there are few reports on myocardial findings of rats and there are hardly any as to comparative reports between electrocardiogram and myocardial findings.

a) Heart weight:

From the second week of deficiency, heart weight started to increase. At the fourth and fifth week it increased markedly and a right heart enlargement was observable. This agrees with the electrocardiographic findings that after 2 weeks, there were more right axis as time progressed. The findings are similar to those of beriberi heart in men.

b) Myocardial findings:

After the 16th day fat increased to a high degree as deficiency progressed, but quickly disappeared after the administration of thiamine. These are noteworthy findings. It has been known that there is a conversion of glucose to fat during glycolysis process when glycolysis is disturbed owing to thiamine deficiency and it is considered that these histological findings show these biochemical changes.

Next, on the cases of the 30th and the 41st day of deficiency, a degeneration was found and this anatomically confirmed our presumption that judging from the recovery speed of electrocardiogram after thiamine administration, electrocardiographic changes are mainly functional before the fourth week of deficiency and are rather organic after that. Furthermore, the appearance of ST or T abnormality in the electrocardiogram owing to myocardial lesions is generally known and it is considered that in the thiamine deficiency electrocardiogram also there is much influence of these histological changes on the ST or T abnormality after the fifth week. At the same time, in the electrocardiographic changes before the fourth week no histological basis was observable whatever, and it was presumed that all were due to biochemical changes. A report on the study of this mechanism will follow later.

Finally, owing to the fact that the concept of "Myocardosis"[21)-22)] is myocardial lesion attributable to general metabolic disturbances, our histo-

logical findings observed in thiamine deficient rats naturally falls under this category. The marked changes caused by the deficiency of thiamine alone are noteworthy. Moreover, it is an important finding that these myocardial degenerations have no connection with the abnormalities of protein metabolism (There was no change in the serum protein fraction. A report on this will follow later). The analysis of these histological changes is a very interesting problem. A further study of this is being continued.

Summary

(1) In the general observations the control normal rats showed no abnormality. On the thiamine deficient rats a definite progress of deficiency symptom was observed and this was quickly normalized by thiamine administration.

(2) In the electrocardiogram of control normal rats, PQ: about 0.05 sec., QRS: within 0.02 sec., T_I: flat, $T_{II, III}$: upright, ST: within 0.1 mV. from base line, and R maximum was 0.2–0.6 mV. The heart rate was 470 to 642 (average 562) and it showed almost negative correlation with body weight. In the electrical axis, the right axis deviation was observed in only 5 cases under 100 Gm. and electrical axis were, for the most parts, normal axis and left axis deviation.

(3) In the electrocardiogram of thiamine deficient rats, during the progress of deficiency, bradycardia, arrhythmia (sinus arrhythmia, a–v block, interpolated nodal rhythm, and premature beat), increase of right axis deviation, ST changes (elevation and depression), and T changes (elevation, depression and negative) were observed.

(4) Thiamine injection on rats of the second to the fourth week of deficiency brought about a marked improvement of the electrocardiographic changes and within a few hours after injection these changes returned to normalcy. But, on the cases of after the fifth week of deficiency the effect of thiamine injection was not so noticeable for several hours. Furthermore, almost no effect of thiamine injection was observed in moribund cases.

(5) The average heart weight of the control normal rats was 409 mg. In thiamine deficient rats the heart weight increased during the progress of deficiency. These cases of increase in heart weight showed a vertical position of the heart in the thorax and a bag shape heart caused by right heart enlargement.

(6) In myocardial findings marked increase of fat granule in myofibrils was found as deficiency progressed. But there was no change in quantity of glycogen. The degeneration began to appear from the 30th day of deficiency and separation of myocardial fibers, granulation of cell plasma, vacuolar degeneration and karyopyknosis were observed. In the

recovery group from thiamine deficiency also, the degeneration was found for about a week.

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Experimental Studies on the Nervous Control of the Renal Circulation

—Effect of the Electrical Stimulation of Splanchnic, Vagal and Other Somatic Nerves and of the Occlusion of Carotid Arteries on the Renal Circulation

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In order to investigate the nervous control of the renal circulation, the renal blood flow was measured by electromagnetic flow meter during the stimulation of the distal cut ends of the splanchnic nerves and the vagal nerve. In addition, the alterations of renal blood flow were observed on carotid occlusion and on stimulation of the proximal end of the divided femoral, sciatic and cervical vagal nerves. The stimulation of the greater and lesser splanchnic nerves produced constriction of renal vessels but the stimulation of the least splanchnic nerve had no effect. The effect of stimulation of the distal end of the vagal nerve to the renal vessels remained unestablished. Carotid occlusion did not influence the renal blood flow. The stimulation of the proximal end of the divided femoral or sciatic nerve may have produced renal vasoconstriction. By the stimulation of the proximal end of the divided vagal nerve, the renal vessels showed various responses with no relation to the alteration in blood pressure. It is a matter of interest that renal vasodilatation may take place in response to vagal afferent stimuli.

IT has been well recognized anatomically that the kidney has an abundant supply of nerve fibers. In spite of vigorous efforts of many investigators, the functional facet of these nerves has not been clarified in details. Also it has not been established definitely whether the renal blood flow remains constant or is variable along with the alterations of systemic circulation in various conditions. It is a matter of interest and is still unknown what a role the nerves in the kidney play in physiologic regulation of renal hemodynamics. In the present study, alterations of renal

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blood flow by the electrical stimulation of the distal cut ends of the nerves which are distributed to the kidney such as splanchnic nerves and vagal nerve are investigated. In addition, changes in renal blood flow are observed under the systemic circulatory changes produced by occlusion of carotid arteries and by electrical stimulation of proximal ends of the vagal, femoral and sciatic nerves in order to clarify the nervous regulatory aspects of renal circulation.

Methods

Experiments were performed on 15 adult mongrel dogs, weighing 8 to 13 Kg., fixed in the supine position and anesthetized with thiopental sodium (20 to 30 mg./Kg.). The systemic arterial pressure was continuously recorded by means of an electromanometer connected to the cannulated femoral artery. The renal blood flow was simultaneously recorded by electromagnetic flow meter which was inserted in a circuit between renal vein and femoral vein. The circuit was made extracorporeally with polyethylene tube, one end of which was inserted into the renal vein close to the kidney and the other into the femoral vein. Thus in this procedure, the direct measurement of the outflow from the renal vein was accomplished continuously throughout the experiment. The renal vascular resistance was calculated by the following equation:

$$\text{Renal vascular resistance} = \frac{\text{mean arterial pressure}}{\text{renal blood flow}} \text{ mm.Hg/ml./min.}$$

$$\text{Mean arterial pressure} = \text{diastolic pressure} + \frac{\text{pulse pressure}}{3}$$

Operations were carried out with a great caution to avoid nerve damage. The ovarian or spermatic vein was ligated. In some experiments the contralateral renal vessels and bilateral adrenal veins were also ligated. The dogs were heparinized prior to closing the circuit to prevent the blood coagulation.

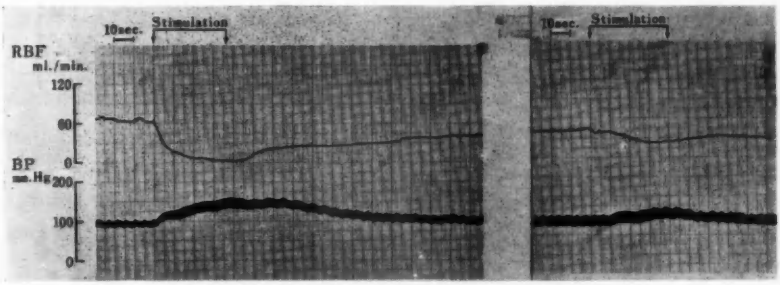
The nerve to be stimulated was prepared free from the surrounding structures carefully and the stem was cut and the peripheral or central ending was kept exposed. Silver electrodes were then placed on the nerve. Electrical stimulation was applied to the distal ends of the divided greater, lesser and least splanchnic nerve and of the divided vagal nerve, in addition to the central ends of the divided femoral, sciatic and vagal nerve. Especially when the splanchnic nerves and the subdiaphragmatic vagal nerve were stimulated, a small mass of semi-liquid paraffin was applied arround the stems to insulate them from the surroundings. The electrical stimuli consisted of rectangular voltage pulses, the duration of a spike was 1 msec., frequency of the pulses 3 to 100 cycles per second, and voltage 0.5 to 30 volts. Each stimulation was continued for 30 seconds.

The carotid occlusion was performed by clamping of bilateral common carotid arteries for 30 seconds.

Results

Greater Splanchnic Nerve Stimulation—

As can be seen in Fig. 1 and 2, electrical stimulation of the divided

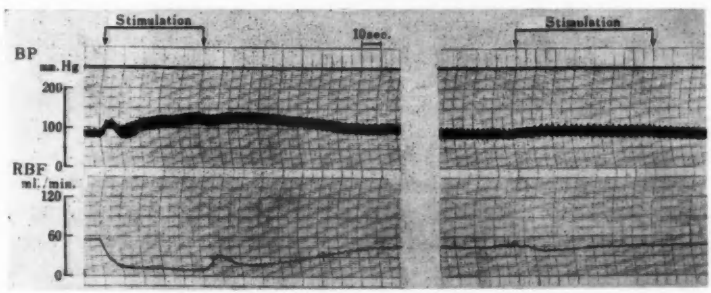


a. b.

Fig. 1. Dog No. 85 Adrenal veins not ligated.

a. Exp. 7 Stimulation of distal end of divided greater splanchnic nerve (30 c/s, 5 V).

b. Exp. 12 The same stimulation after intravenous injection of 10 mg. of regitine.



a. b.

Fig. 2. Dog No. 90 Bilateral adrenal veins were ligated.

a. Exp. 1 Stimulation of distal end of divided greater splanchnic nerve (30 c/s, 3 V).

b. Exp. 5 The same stimulation after intravenous injection of 1.2 mg. of hydergine.

greater splanchnic nerve on the distal end produced uniformly a rise in systemic arterial pressure and a simultaneous decrease in renal blood flow in all 23 experiments. The calculated renal vascular resistance increased markedly. The elevation of mean arterial pressure ranged from 8 to 66 mm.Hg with an average of 26 mm. Hg (10% to 76%, mean 35%). The decrease in renal blood flow was 15 to 82 ml./min. with a mean of 42 ml./min. (15% to 97%, mean 52%). The change in renal vascular resistance was 2.1 to 48.6 times (mean 8.0 times) as high as the control level. On many occasions two phases could be distinguished in the pressor response; in the first phase (in 5 to 10 sec.) a rapid rise of blood pressure took place immediately after the onset of stimulation and then the pressure either came down shortly or was maintained at this elevated level; in the second

phase (10 to 20 sec. later) the pressure rose more slowly again and maintained the high level until the release of stimulation. On the other hand, renal blood flow decreased abruptly and markedly with stimulation and changes in such two phases as observed in blood pressure responses were not recognized.

Lesser Splanchnic Nerve Stimulation—

Fig. 3 shows typical response to the stimulation of the lesser splanchnic

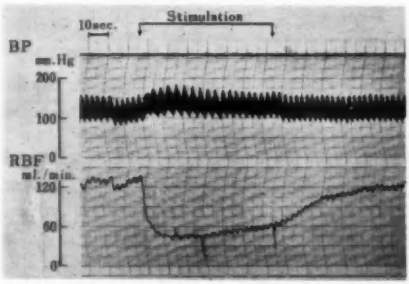


Fig. 3. Dog No. 82 Adrenal veins not ligated.
Exp. 4 Stimulation of distal end of divided lesser splanchnic nerve (30 c/s, 7 V).

nerve on the distal end. The systemic arterial pressure rose and the renal blood flow decreased markedly in 6 experiments on 2 dogs. The magnitude of hypertensive responses ranged from 9 to 31 mm.Hg with a mean value of 18 mm.Hg (7 to 27%, mean 16%), and the decrease in renal blood flow from 57 to 111 ml./min. with a mean of 80 ml./min. (43 to 84%, mean 69.1%). The renal vascular resistance was 1.8 to 6.7 times (mean 4.5 times) as high as the control level. The pressor response did not show any two-phase pattern as seen in the greater splanchnic nerve stimulation.

Least Splanchnic Nerve Stimulation—

With the stimulation of the least splanchnic nerve in 4 dogs, neither constant nor significant responses of both systemic arterial pressure and renal blood flow were observed.

In the experiments of the greater or lesser splanchnic nerve stimulation, it was apparent that the elevation in blood pressure and the fall in renal blood flow were more striking as the stimulation became stronger in voltage within the range of 1 to 10 volts. There was no difference in the responses whether the adrenal veins of the dog were ligated or not (Fig. 1 and 2), and also whether the dog was vagotomized or not. These responses to the splanchnic nerve stimulation were inhibited or depressed after intravenous injection of 10 mg. of regitine® (Fig. 1) or 0.3 to 1.2 mg. of hydergine® (Fig. 1 and 2).

Efferent Vagal Nerve Stimulation—

Stimulation of the distal end of the divided cervical vagus produced a prompt fall in blood pressure with cardiac arrest or bradycardia and a

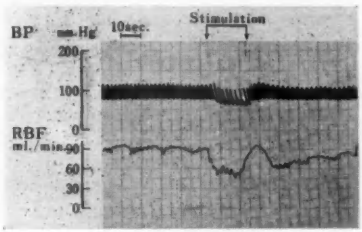


Fig. 4. Dog No. 84
Exp. 14. Stimulation of distal end of divided cervical vagal nerve (5 c/s, 3V).

decrease in renal blood flow in all 12 experiments on 6 dogs (Fig. 4). The renal blood flow began to recover during stimulation in spite of persistence of the fall in blood pressure, and it decreased again after release of the stimulation, later slowly recovering to the value before the stimulation.

Subdiaphragmatic vagal nerve was stimulated on the distal end in 8 experiments on one dog. The less hypotensive response without bradycardia or cardiac arrest and less decreased renal blood flow were observed. The changes of the calculated renal vascular resistance were not significant (Fig. 5).

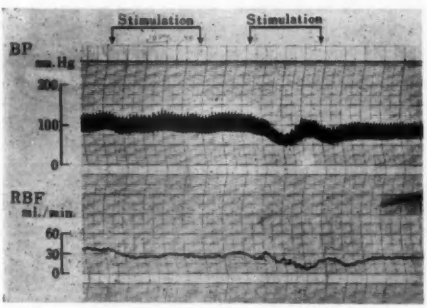


Fig. 5. Dog No. 81
Exp. 2. Stimulation of distal end of divided subdiaphragmatic vagal nerve (30 c/s, 5V).
Exp. 3. Stimulation of distal end of divided subdiaphragmatic vagal nerve (30 c/s, 10V).

Carotid Occlusion—

In 7 experiments on 4 dogs which showed 10 to 24 mm. Hg rise in systemic blood pressure by the occlusion of common carotid arteries, the

alterations in renal blood flow were not significant in all experiments (−5

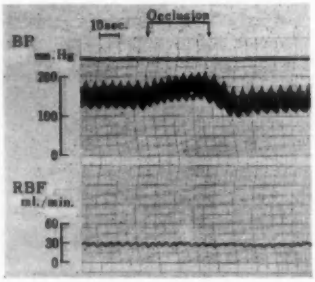


Fig. 6. Dog No. 105
Exp. 17 Occlusion of bilateral common carotid arteries.

to +2 ml./min.). Fig. 6 shows such an example. The renal vascular resistance increased slightly in all cases. The rate of increase ranged from 7.4 to 18.1% with an average of 12.2%.

Afferent Stimulation of Femoral or Sciatic Nerve—

By stimulating proximal end of the divided femoral or sciatic nerve in 10 dogs caused either hypertensive or hypotensive response. The renal blood flow decreased more or less in either response in blood pressure.

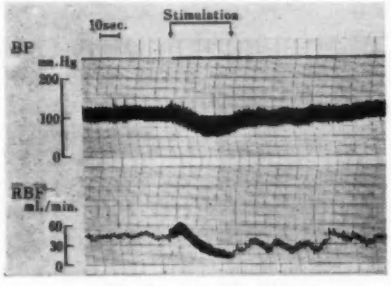


Fig. 7. Dog No. 102
Exp. 1 Stimulation of proximal end of divided femoral nerve (50 c/s, 3V).

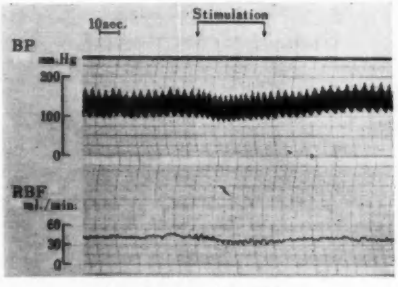


Fig. 8. Dog No. 105
Exp. 13 Stimulation of proximal end of divided sciatic nerve (50 c/s, 20V).

Fig. 7 and 8 show a decrease in renal blood flow accompanied by hypotensive response, in femoral and sciatic nerve stimulation respectively. Fig. 9 is an example which showed a decrease in renal blood flow with hypertensive response. The response was hypertensive (7 to 22 mm. Hg) in 10 experiments and hypotensive (7 to 36 mm. Hg) in 12 cases. No essential difference was found between the stimulations of the femoral and sciatic nerve. In 4 dogs, high voltage stimulation produced hypertensive response

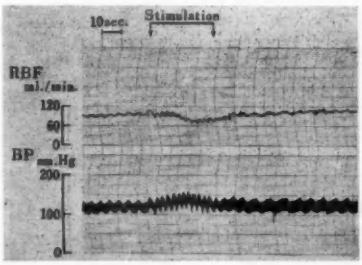


Fig. 9. Dog No. 109
Exp. 4 Stimulation of proximal end of divided sciatic nerve (50 c/s, 20V).

and low voltage stimulation produced hypotensive response, whereas in 2 dogs response was always hypertensive and in 4 dogs hypotensive in any applied conditions. In addition, it was observed in hypertensive response that the elevation in blood pressure was produced more strikingly by the stimulation with higher voltage.

The decrease in renal blood flow was variable, maximum of 32 ml./min. (56.1%) to minimum of 3 ml./min. (6.1%), and generally slight in degree (mean: 10 ml./min., 23.8%). In 5 of 8 experiments with femoral nerve stimulation and in 8 of 14 experiments with sciatic stimulation significant alterations in renal blood flow (over 8 ml./min.) were recorded. In 9 experiments, the renal blood flow did not show any significant change in spite of alteration of the blood pressure.

The renal vascular resistance increased significantly in 13 experiments. The rate of increase ranged from 20 to 140% with an average of 38.4%. Even in hypotensive response, the calculated vascular resistance was increased. As a rule, the fall in renal blood flow and the rise in renal vascular resistance were more striking as stimulation became stronger in voltage.

Afferent Cervical Vagal Nerve Stimulation—

By stimulating the proximal end of divided cervical vagal nerve, pressor, depressor or biphasic response occurred. Four dogs showed only hypotensive or only hypertensive response in any condition of stimulation and 3 dogs showed hypotensive response in low voltage and hypertensive response in high voltage.

The renal blood flow also varied and its change was not always related to the change in blood pressure. Fig. 10 shows the biphasic response in renal blood flow associated with hypertensive response. Fig. 11 is an example of increased renal blood flow with hypotensive response. Fig. 12 shows a decrease in renal blood flow accompanied by hypotensive response. In 17 experiments with hypertensive responses ranging from 11 to 55 mm. Hg (mean 21 mm. Hg, 30.8%), the renal blood flow increased by 3 to 27 ml./min. with an average of 8.9 ml./min. (23.8%) in all but 2 cases

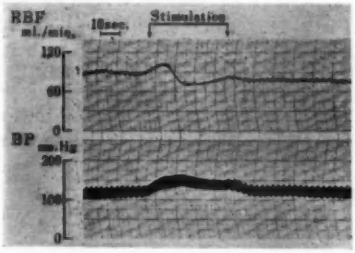


Fig. 10. Dog No. 109
Exp. 15 Stimulation of proximal end of divided cervical vagal nerve (50 c/s, 30V).

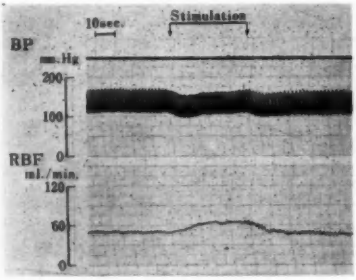


Fig. 11. Dog No. 108
Exp. 7 Stimulation of proximal end of divided cervical vagal nerve (100c/s, 20V).

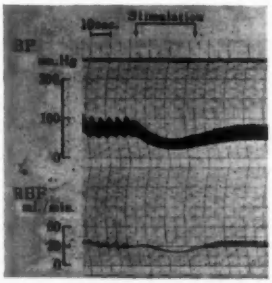


Fig. 12. Dog No. 105
Exp. 8 Stimulation of proximal end of divided cervical vagal nerve (50 c/s, 15V).

with biphasic changes. In only 9 experiments, however, these changes were significant. In 16 experiments with hypotensive responses ranging from 9 to 43 mm. Hg (mean 17 mm. Hg, 22.9%) the renal blood flow increased in 6 (mean 13 ml./min., 31.6%) and decreased in 4 (mean 8 ml./min., 22%). In the remainder it did not change significantly. One biphasic response in blood pressure was accompanied by a biphasic change in renal blood flow.

The changes in renal vascular resistance were much variable and had no relation to the alterations in blood pressure. The renal vascular resistance increased in 6, decreased in 2, did not change in 9 cases with hypertensive response and increased in 2, decreased in 11, did not change in 3 with hypotensive response and did not change in a case with biphasic response in blood pressure. It could not be found in this study, that the changes in renal blood flow and in renal vascular resistance had any relation to the voltage or to the frequency of the stimulant pulses.

Discussion

The regulation of renal circulation is carried out by nervous and hormonal control as well as by autoregulatory mechanism. The kidney is supplied with nerves mainly by the way of the renal plexus communicated with the greater and lesser splanchnic nerves and the vagal nerve.[1,2]

On the effect of direct renal nerve stimulation, Study and Shipley[3] reported 53% average decrease in renal blood flow measured by a rotameter. Houck[4] observed reduction in renal blood flow, glomerular filtration rate and urine flow. On the effect of splanchnic nerves, Nakayama,[5] one of authors, also reported a decrease in renal blood flow and glomerular filtration rate with an average of 88.4% and 86.3% respectively, by the methods of renal clearance, renal vein catheterization and renal vein cannulation. In the present study the greater, the lesser and the least splanchnic nerves were stimulated separately, to observe the difference of renal innervation among these nerves. For the alterations of systemic arterial pressure, the stimulation of the greater splanchnic nerve was the most effective, that of the lesser splanchnic nerve was less, and of the least splanchnic nerve not effective. On the effect to renal blood flow, the stimulation of the greater splanchnic nerve decreased it as markedly as the lesser splanchnic nerve, although the least splanchnic nerve had no significant effect. These results suggest that the greater splanchnic nerve has more wide distribution of its nerve endings to vascular beds including the kidney than the lesser splanchnic nerve which has a distribution relatively confined to the kidney and the least splanchnic nerve supplies scarecely vasoconstrictive fibers to the kidney. The decrement of 52 or 69.1% in renal blood flow in our electromagnetic flow meter method was in complete accordance with the 53% decrease in rotameter method reported by Study and Shipley.[3] These effects of splanchnic nerve stimulation were not influenced by ligation of the adrenal veins. This indicates that the responses to stimulation of splanchnic nerves were produced rather directly by neural than hormonal effect. Regitine and hydergine depressed or inhibited the effect of the splanchnic nerve stimulation and vascodilatatory effect by stimulation of splanchnic nerves could not be observed even after an injection of such adrenolytic substances.

It has been demonstrated anatomically that vagal nerve is distributed in the kidney [2] but its role in renal circulatory regulation is not quite clear. Burton-Opitz and Lucas[6] concluded in their report that the vagi do not embrace nerve fibers by means of which the vascularity of the kidney may be altered. In our study, the renal blood flow was markedly reduced with hypotensive response and bradycardia by the distal stimulation of the divided vagal nerve of the cervical portion. Its change is considered to be mainly due to decrease in cardiac output. But, further,

even in the distal stimulation of vagal nerve amputated at the subdiaphragmatic portion to avoid the cardiac effect, systemic arterial pressure fell and renal blood flow decreased. It could not be concluded yet because the results were obtained in only one dog with subdiaphragmatic vagal nerve stimulation and the changes in calculated renal vascular resistance were not significant.

Many authors have described that the renal blood flow remains constant while systemic arterial pressure alters whithin a physiological range.[7] To study whether renal blood flow is maintained at a constant level or not in various conditions, electrical stimuli on the proximal ends of divided sciatic, femoral and vagal nerves and carotid occlusion were applied in this study.

In carotid sinus reflex, Heymans[8] found a decrease and Kigawa[9] observed a slight increase in renal blood flow. On the other hand, the curious independence of the renal blood flow was reported in hypertensive response by Rein[10] and was also observed in hypotensive response by Opitz and Smith.[11] Unna[12] described no detectable influence on the renal blood flow in hypertensive response due to clamping both carotids and in hypotensive response due to distension of one carotid sinus. In our study, in hypertensive response to carotid occlusion, the renal blood flow did not alter as Rein reported. The calculated renal vascular resistance increased slightly. Engelhorn[13],[14] described that nerve impulse obtained from renal nerve in cats increases with elevation in blood pressure by carotid occlusion. Therefore, it is considered that in carotid occlusion renal vessels may constrict so slightly by neural control as renal blood flow shows no change.

During the stimulation of the central ends of the sciatic nerve, Roy[15] and Bradford[16] observed well-marked contraction of kidney by oncometric records. Recently, Kigawa[9] reported that the renal blood flow decreased in most of the experiments with hypertensive response and its decrement was greater in higher voltage stimulation by the method of electromagnetic flow meter. Burton-Opitz and Lucas,[6] however, described that the renal blood flow remains practically unaltered by measurement of thermostromuhr. In this study by electromagnetic flow meter measurement, the renal blood flow did not change or decreased and the renal vascular resistance increased in either hypertensive or hypotensive response to the stimulation of proximal ends of femoral or sciatic nerve. It should be noted that the change in renal blood flow is not directly related to the alteration in blood pressure but is related to voltage of applied stimulation. This fact indicates that in the stimulation of central femoral or sciatic nerve the renal blood flow is influenced by a neuro-reflexive effect, probably mediated by the central nervous system such as spinal cord, rather than by alterations in systemic arterial pressure and the attitude of renal

vascular vessels attributes little to elevation or reducation in blood pressure.

On the effect of the stimulation of the afferent cervical vagal nerve on renal blood flow, Bradford described that the kidney volume decreased by stimulation of this nerve. Burton-Opitz[8] observed that no change in renal blood flow occurred even at a time when the very pronounced rises in arterial blood pressure had fully developed. By Kigawa[9] the alteration in renal blood flow was indicated to be various, though the hypertensive response was generally accompanied by the renal vasoconstriction. Quite various results in blood pressure and in renal blood flow were obtained in this study. The renal blood flow remained unaltered in 14 of 33 experiments in spite of the change in blood pressure. When any change in renal blood flow was observed, the renal blood flow was not always related to the blood pressure. In hypertensive responses, the renal blood flow usually increased but in hypotensive responses the change in renal blood flow was various. Also the calculated renal vascular resistance was various and not related to the blood pressure. The alterations of renal blood flow and renal vascular resistance were independent of the conditions of stimulation such as voltage and frequency. This result is different from that of the afferent stimulation of femoral or sciatic nerve.

It is of interest that in some hypotensive responses the renal blood flow increased and the renal vascular resistance was reduced. This fact suggests that the afferent stimulation of the vagal nerve may produce vasodilatation in renal vessels.

Although carotid occlusion, the afferent stimulation of the divided vagal, and femoral or sciatic nerves were applied in order to observe the changes in renal blood flow in the alterations of systemic arterial pressure, it was apparent that obtained results could not be discussed uniformly because these procedures might have some specific influences, if any, to the renal vessels. It is, however, not clear what a mechnism produces such specific effects.

Summary

By means of electromagnetic flow meter the alterations of renal blood flow were observed in dogs in various conditions, to study nervous control of renal circulation, and following results were obtained.

(1) In electrical stimulation of the distal end of the divided greater and lesser splanchnic nerves, the systemic blood pressure rose and the renal blood flow decreased.

(2) In stimulation of the distal end of the divided least splanchnic nerve, no change in blood pressure and in renal blood flow was observed.

(3) In stimulation of the distal end of the divided cervical vagal nerve, the renal blood flow decreased with bradycardia or cardiac arrest.

In stimulation of the subdiaphragmatic portion, the blood pressure fell and the renal blood flow decreased slightly.

(4) In hypertensive response due to the occlusion of common carotid arteries, the renal blood flow did not change.

(5) In stimulation of the proximal end of the divided femoral or sciatic nerve, the renal blood flow did not change or decreased in either hypertensive or hypotensive response.

(6) In stimulation of the proximal end of the divided cervical vagal nerve, changes in blood pressure and in renal blood flow were various. The alteration of renal blood flow was related neither to the change in blood pressure nor to the conditions of stimulation.

Acknowledgement

The authors wish to express their thanks to Mr. S. Ushiama for his excellent technical assistance throughout this experiment.

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Circulatory and Respiratory Effects of Hypertonic Saline with Special Reference to the Coronary Effect

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In an attempt to elucidate the mechanism of the systemic hypotension produced by the rapid intravenous injection of 20 per cent saline, experiments were made using the intracoronary injection technique and transeptal left atrial puncture in a total of 25 dogs. Accompanying apnea and bradycardia were considered to be due to the pulmonary reflex via the vagus. Scrutiny of systemic hypotension produced after injection of hypertonic saline into varying cardiovascular chambers showed that the injection into the left side of the heart also resulted in the same degree of hypotension as that of the right side, and that pressure fall was separated into early and late dips, about which the genesis was discussed and the former was attributed to the coronary effect. Electrocardiographic analysis revealed that the ST and T changes were the proof of the arrival of saline at the coronary circuit and their mechanisms were mentioned. From these results the authors emphasized the possible role of coronary effect by the agent and suggested the transient myocardial failure in the production of systemic hypotension.

IT is now evident that the rapid intravenous injection of hypertonic saline produces the triad, namely systemic arterial hypotension, apnea and bradycardia.[1)-10)] Although the apnea and bradycardia are considered to be produced by a reflex mechanism mediated via the vagus nerve, there is no agreement about the mechanism of the arterial hypotension.[2),5)-10)] The purpose of this paper is to present our experiences about the hemodynamic responses and electrocardiographic changes induced by the intravenous injection of hypertonic saline, and to discuss the results in comparison with previous studies. To maintain the animals in the best physiological condition, our experiments were performed in closed-chest dogs with the aid of transeptal left atrial puncture and intracoronary injection technique.

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Materials and Methods

Twenty-five mongrel dogs each weighing between 7.5 and 15 Kg. were anesthetized with morphine (4 to 5 mg./Kg.) and chloralose (50 mg./Kg.) or amobarbital sodium (60 mg./Kg.). With the aid of fluoroscopy, a cardiac catheter was introduced into the main pulmonary artery via the right external jugular vein, and similar catheters were also inserted into the femoral artery and the inferior vena cava. The injection of hypertonic saline and pressure recording in the left atrium were made by puncturing the interatrial septum from the right atrium as described by Ross and his associates.[11),12)] In some of the experiments, the intracoronary injection was performed with special catheter introduced into the circumflex branch of the left coronary artery.[13),14)] The location of the catheters was verified at the end of the experiments. Blood pressures were measured by 2 electromanometers, and the systemic and pulmonary arterial pressures were recorded on a 3-channel direct writer with electrocardiogram. Arterial pressure was also recorded on the sooted paper of the kymographion and at the same time the pulmonary arterial pressure was recorded with the left atrial pressure on a direct writer.

Five to 10 ml. of 20 per cent solution of sodium chloride (0.5 to 1 ml./Kg.) was injected through the catheter into the various parts of the cardiovascular system in 2 to 5 seconds. A total of 191 injections were made: 42 into the inferior vena cava or femoral vein, 49 into the pulmonary artery (partly into the pulmonary capillary), 20 into the left atrium, 3 into the left ventricle, 41 into the aorta (including 19 into the ascending aorta, 3 into the aortic arch, 10 into the descending aorta or femoral artery, and 9 into the carotid artery), and 19 into the coronary artery. In the last group, the dose of solution injected was 0.5 to 1 ml. of 10 per cent saline.

Control experiments with the same quantities of normal saline and a 50 per cent solution of glucose were performed in a total of 17 injections: 12 with normal saline and 5 with glucose.

Results

(I) Control Experiments.

The injections of normal saline into the various parts of the cardiovascular system were followed by changes neither in the systemic arterial, pulmonary and left atrial pressures nor in respiration and electrocardiogram. The injections of 50 per cent glucose resulted in no changes in all experiments but one, in which a slight arterial hypotension was produced after intravenous injection.

(II) Changes in Systemic Arterial Pressures.

A total of 29 injections were made into the inferior vena cava of 18 dogs, which were followed within 3 to 8 sec. (average 5 sec.) by a fall of arterial pressure. There were usually 2 phases of pressure fall, the first was reached within 10 to 15 sec. and averaged 20 mm.Hg; the second

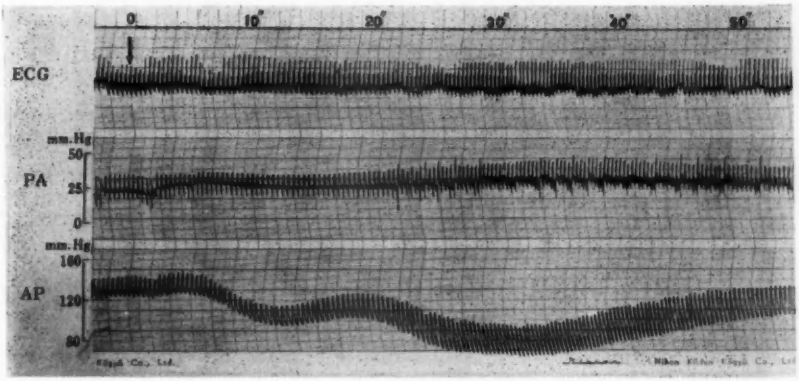

Fig. 1. Changes in pressure of pulmonary artery and systemic artery following the intravenous injection of 10 ml. of 20 per cent saline. Arrow indicates the time of injection.

was at about 40 sec. after injection and averaged 40 mm.Hg (Fig. 1). The difference in anesthesia did not influence the characteristic responses. The arterial pressure returned to the original level within 2 to 3 minutes. In 6 of 29 injections (about one fifth), the first and second fall fused to one deep depression. The hypotension was not influenced at all by the bilateral cervical vagotomy which was performed in a total of 13 experiments (Fig. 2).

The basic pattern of the pressure fall after the intravenous injection was not changed when the injection was made into the pulmonary artery, left atrium (Fig. 2, B), and left ventricle. However, the interval between the injection and the beginning of the systemic hypotension was shorter when the injection was made into the left atrium than into the pulmonary artery; in the former it averaged 1.7 and in the latter 3.4 sec.

(III) Changes in Pulmonary Arterial and Left Atrial Pressures.

Pulmonary hypertension, which corresponded in time to the first fall of the systemic arterial pressure, was seen in only 16 of 42 injections into the inferior vena cava (Fig. 3). The other pressure patterns of pulmonary artery were hypertension seen at the time of the second fall of arterial pressure in 12 instances and no changes in 14. The 3 different patterns of the pulmonary arterial pressure were of about similar incidence (Fig. 4).

Simultaneously recorded left atrial pressure demonstrated no constant tendency of the change; some increased, some decreased and the rest remained unchanged. The characteristic pattern described by Eliakim et al.,[7] which showed the increased pulmonary arterial pressure and the decreased left atrial pressure, was seen in only 4 instances (about 10 per cent). Fig. 5 shows the case with a slight increase in left atrial pressure.

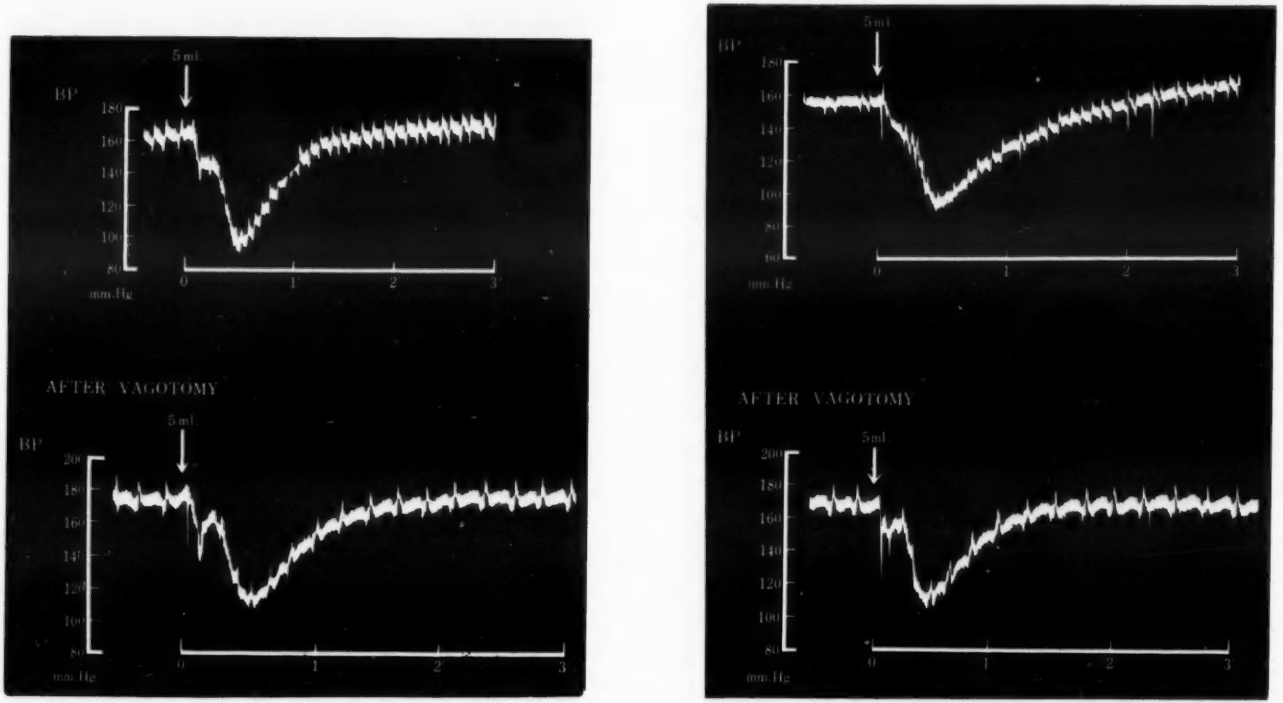

Fig. 2. Systemic arterial hypotension following the injection of 20 per cent saline into the inferior vena cava (A) and the left atrium (B) before and after bilateral cervical vagotomy.

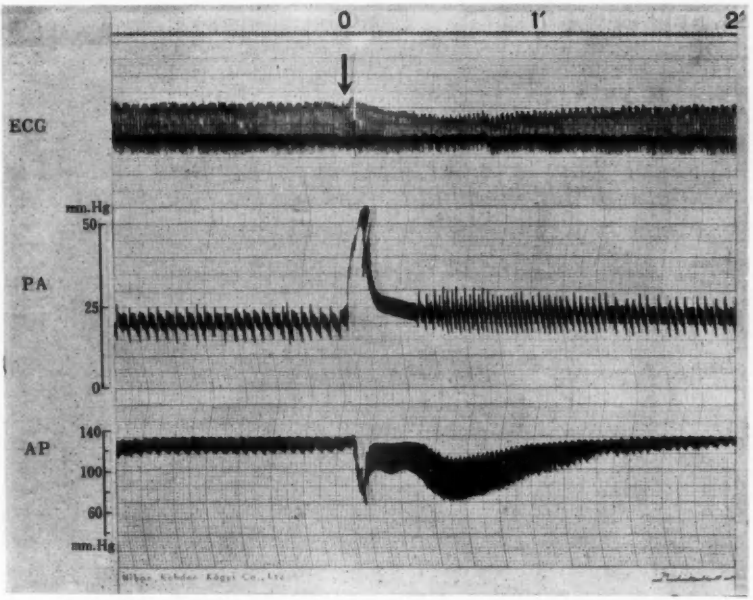

Fig. 3. Changes in pressure of pulmonary artery and systemic artery following the intravenous injection of hypertonic saline. Note the marked pulmonary hypertension.

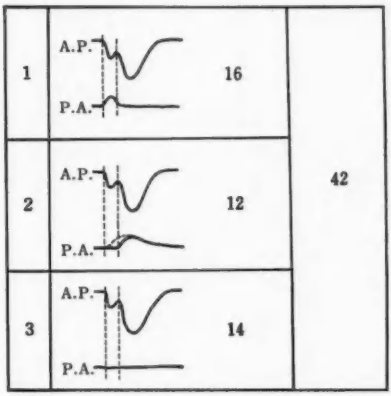

Fig. 4. Incidence of the pressure patterns of pulmonary artery, in relation to the biphasic hypotension of the systemic artery when injections were made into the inferior vena cava in a total of 42 instances.

A.P.: systemic arterial pressure.
P.A.: pulmonary arterial pressure.

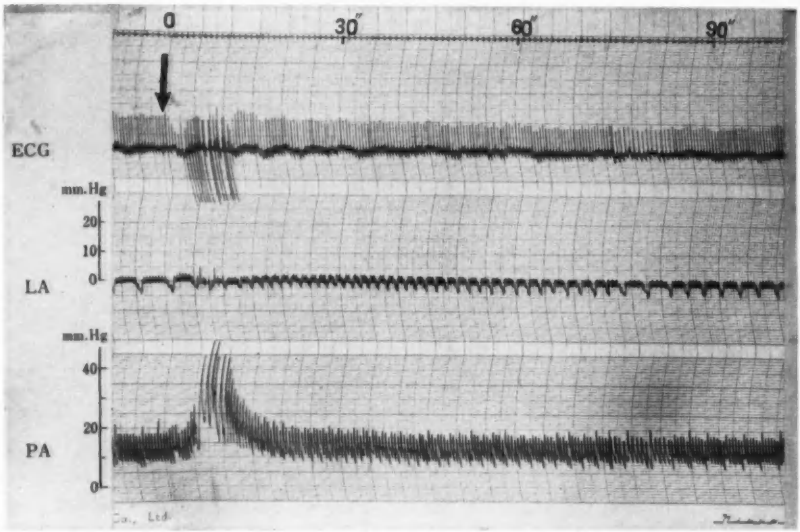

Fig. 5. Changes in pressure of pulmonary artery and left atrium following the intravenous injection of 5 ml. of 20% saline.

When the hypertonic saline was injected into the pulmonary artery, the pressure patterns were approximately the same as those after the injection into the inferior vena cava. The pulmonary hypertension associated with the first fall in arterial pressure was observed in 27 of 49 injections (about 55 per cent), of which simultaneous left atrial pressure fall was observed in only 2 instances. Left atrial pressure was seen to remain the same in 10 cases and to increase in 10 others.

When the injections were made into the left atrium, pulmonary arterial pressure did not show any change in 14 instances and increased in 6. The magnitude of pressure increase was within 10 mm.Hg in 4 and about 20 mm.Hg in 2 other experiments.

(IV) Intracoronary Injection.

The concentration of the injected saline varied widely, but in most cases a 10 per cent solution was used in a dose of 0.5 to 1 ml. The systemic arterial pressure began to fall immediately after the injection, reaching its nadir in about 3 sec. in the fastest cases. The magnitude of the pressure decrease was 70 to 80 mm.Hg in the most marked cases. The second fall of the systemic arterial pressure was not observed. The depressor effect was more prominent in the 0.5 ml. of 20 per cent solution than the 1.0 ml. of 10 per cent solution. One of these experiments was shown in Fig. 6. Vagotomy did not influence the hypotension.

When the injection was made into the lower part of the ascending

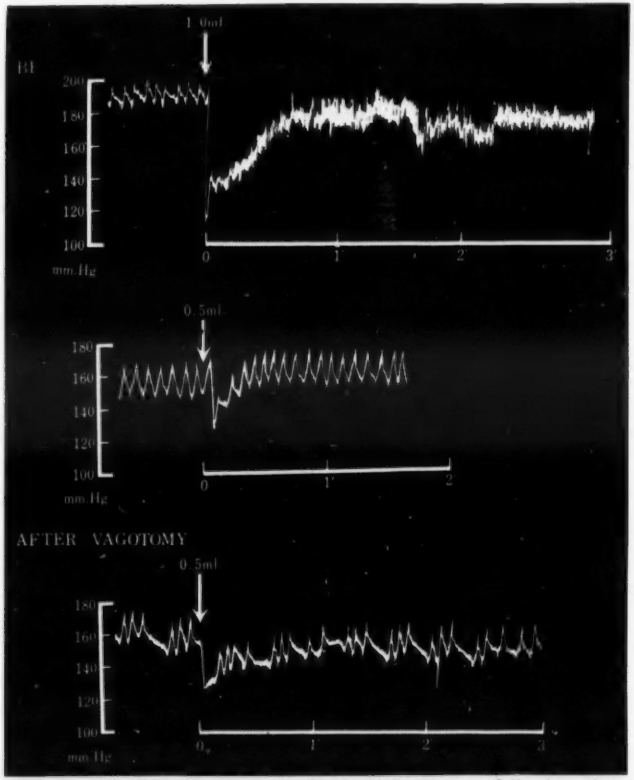

Fig. 6. Changes in systemic arterial pressure following the intracoronary injection of 10 per cent saline.

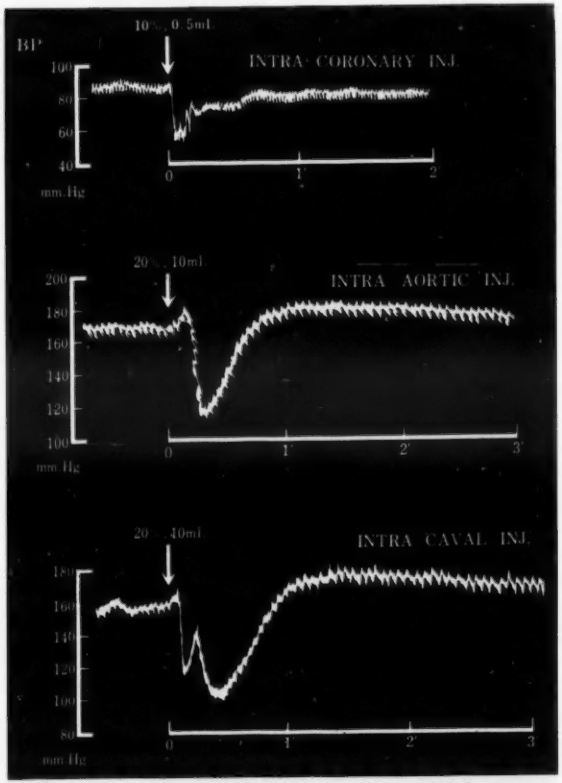

Fig. 7. Comparison of the systemic arterial hypotension following injection into the coronary artery, upper part of the ascending aorta and the inferior vena cava.

aorta near the ostium of the coronary artery, the pressure changes were similar to those observed after the intracoronary injection. Injection into the upper part of the ascending aorta or into the more distal part of the aorta resulted in a delayed hypotension as compared with the changes by the intracoronary injection (Fig. 7).

(V) Electrocardiographic Changes.

Bradycardia was always seen after the injection of hypertonic saline into the inferior vena cava and pulmonary artery, but not into the left atrium, left ventricle, coronary artery and aorta (Fig. 8). When injected into the

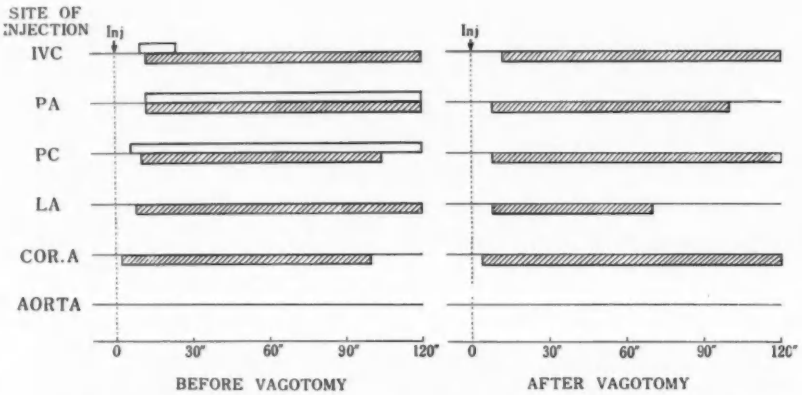

Fig. 8. Illustration of the electrocardiographic changes following the injection of the hypertonic saline into the varying sites of the cardiovascular system. Open area indicates duration of bradycardia, hatched area that of ST, T changes.

inferior vena cava, bradycardia appeared about 5.5 sec. after the injection and continued for 3 to 30 sec. (average 13 sec.). Injection into the pulmonary artery resulted in bradycardia within 2 to 8 sec. (average 4 sec.). The duration of the bradycardia was 30 sec. to 2.5 minutes (average 56 sec.), which was more prolonged than that by the injection into the inferior vena cava. The degree of bradycardia was a decrease of 6 to 18 beats per minute in the case of intravenous injection, and 6 to 100 beats per minute in the case of intrapulmonary injection. In general, the dogs anesthetized with morphine-chloralose showed more prominent bradycardia than those anesthetized with amobarbital sodium.

ST-segment and T-wave abnormalities occurred in all instances of the injection except for the cases where the injection was made into the upper part of the ascending aorta and its distal portion (Fig. 8). ST-segment changes were almost always depression, and rarely elevation. These changes reversed to the control level within 1 to 2 minutes, but when the injections

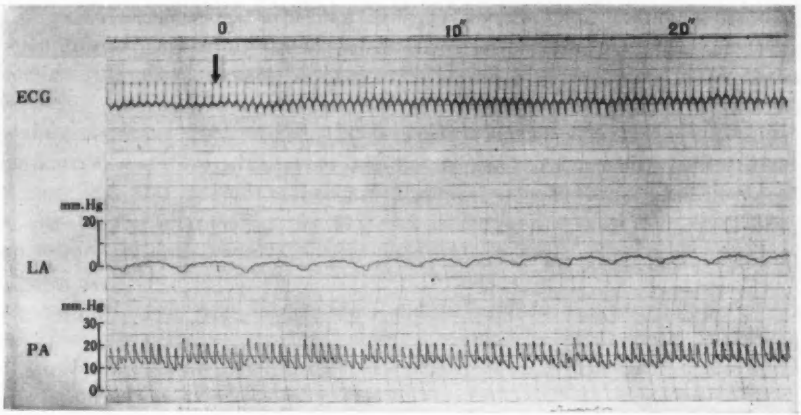

Fig. 9. Changes in electrocardiogram, pressure of left atrium and pulmonary artery following the intracoronary injection of 1 ml. of 5% saline.

were repeated over several times in the same dog, the changes became irreversible, and resulted in sustained ST and T changes. The time interval from the injection of hypertonic saline to the occurrence of the ST, T changes were 3 to 15 sec. (average 6 sec.) in the instance of inferior vena cava, 3 to 10 sec. (average 5 sec.) in the pulmonary artery, 1 to 7 sec. (average 3.6 sec.) in the left atrium, and 1 to 3 sec. (average 2 sec.) in the left coronary artery (Fig. 9). These ST and T changes occurred earlier than or simultaneously with the onset of systemic arterial hypotension.

Decreased voltage of the P-wave appeared earlier than the occurrence of bradycardia, and was present in almost all cases of the injection into the inferior vena cava, pulmonary artery and left atrium, but not in cases of injection into the left ventricle. Its duration and intensity did not show any uniformity and the difference due to the sites of injection was not so remarkable as the bradycardia.

The amplitude of the R-deflection was increased within 10 sec. after the injection of hypertonic saline into the cardiac cavities, irrespective of left or right heart, and partly followed by a decrease in amplitude. Intracoronary injection revealed no changes in P-wave, no increase in R-deflection, and some showed a decrease in the amplitude of R-deflection.

There were no remarkable changes in PR-interval or QRS duration.

Arrhythmias most frequently observed were atrial and/or ventricular premature systoles, which were in short run within 10 sec. after the injection, or in frequent occurrence after about 20 to 30 sec. Differences due to the sites of injection were not found. In one dog the 6th injection of hypertonic saline made into the left atrium, resulted in ventricular

fibrillation and death. Paroxysmal tachycardia was observed in 2 other dogs. In the dogs anesthetized with morphine-chloralose, second degree atrioventricular block was often seen, which returned to a sinus rhythm after the injection.

In the bilaterally vagotomized dogs, bradycardia was completely eliminated regardless of different anesthetics. The other electrocardiographic changes, however, were not influenced.

(VI) Respiratory Changes.

The remarkable sign of respiratory effect produced by hypertonic saline was apnea. It appeared immediately after the injection into the inferior vena cava and the pulmonary artery and was considerably prolonged, but did not appear after the injection into the left atrium or into the coronary artery (Fig. 10). Similar to the bradycardia, apnea was also

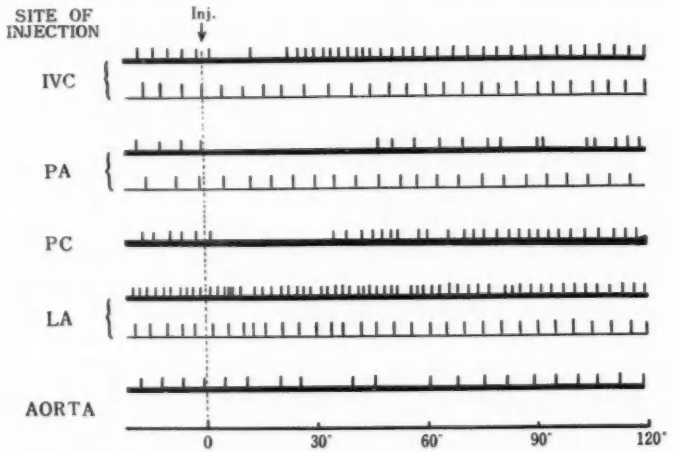

Fig. 10. Changes in respiratory rate following the injection of hypertonic saline into the varying sites of the cardiovascular system, before and after bilateral cervical vagotomy. Upper trace indicates the changes before vagotomy, lower trace after vagotomy. Each vertical bar indicates one respiratory movement.

completely abolished by the vagotomy. No difference was found in the character of the apnea between the 2 different kinds of anesthetics. After an injection of hypertonic saline into the ascending aorta, apnea was also observed, and occurred in the delayed period.

Discussion

In the present series bradycardia and apnea occurred only when the injection of hypertonic saline was made into the right side of the heart but

not in the left side; the effect was especially prominent in the injection into the pulmonary artery; vagotomy completely eliminated both effects; all these findings indicated the 2 responses to be effectuated by a pulmonary reflex via the vagus nerve. The systemic hypotension was not influenced by the vagotomy, and so the above responses were not consistent with the known reflexes,[15] which include coronary chemoreflex, pulmonary depressor chemoreflex, and pulmonary depressor reflex mediated by baroreceptor.[16]

As for the changes in the arterial pressure, injection into the inferior vena cava, pulmonary artery, and left atrium was followed in a similar pattern by the biphasic pressure fall; the second fall was deeper than the first, and in some experiments two falls fused into one. These findings are in agreement with the previous works by Binet,[4]-[6] Muirhead,[2] Eliakim[7] and Semler,[10] although the trials of injection into the left atrium were not so found in the past. Its interpretations, however, were different. Binet and Burstein showed that pulmonary hypertension occurred shortly before the systemic hypotension and explained this by the "barrage pulmonaire" induced by the pulmonary arteriolar spasm. Eliakim and his associates observed simultaneous decrease in left atrial pressure and concluded that the systemic hypotension was caused by the spasm of the pulmonary vein-left atrial junctional muscle. He suggested the presence of a kind of receptor, sensitive to high concentrations of Na^+ and/or Cl^-. On the other hand, Semler demonstrated that the pressure gradient occurred between the pulmonary artery and its distal vessels and that the pulmonary block should be produced in the proximal portion to the site which was suggested by Eliakim. Read and his associates[8],[9] showed that the triad did not occur in a preparation perfused with a solution devoid of erythrocytes. They showed that in the perfused lung erythrocytes agglutinated transiently within 5 to 10 sec. after the injection and raised the vascular resistance, and that the vascular spasm did not occur and blood flow recovered within 60 sec.

In the present experiments when the injections were made into the inferior vena cava and pulmonary artery (91 times), the pulmonary arterial pressure increased markedly in 43 instances (Fig. 3), of which only 6 showed a decrease in left atrial pressure. Although there were few cases which were in agreement with Eliakim's pattern, about one-half of the experiments demonstrated pulmonary hypertension which shortly preceded the systemic hypotension. The remaining one-half, however, did not show significant pulmonary hypertension. In addition, similar hypotension was reproduced even by injecting hypertonic saline directly into the left atrium and left ventricle not through the pulmonary circuit. These sorts of experiment have not been done except for that of Binet[5],[6] and Muirhead.[2] Binet observed arterial hypotension by the injenction of hypertonic saline into the left atrium. Muirhead showed a systemic hypotension of 34 mm. Hg on aver-

age after the injection of 50 per cent glucose into the left ventricle. Furthermore, the ST and T changes in ECG appeared almost simultaneously with systemic hypotension and when the site of injection was nearer to the coronary ostium, appearance of ST and T changes occurred earlier. These facts strongly suggested the presence of other factors besides the pulmonary block in the production of systemic hypotension, and led us to examine the effects of intracoronary injection of hypertonic saline.

The intracoronary injection of hypertonic saline was followed immediately by monophasic systemic hypotension, which is consistent with the previous work. A small dose (0.5 to 1.0 ml.) of 10 per cent solution into the coronary artery was sufficient to produce the same degree of hypotension as that by intravenous injection. This dose was smaller than that of Muirhead,[2] which was in the range of 0.23 to 0.70 ml./Kg. Injection into the upper part of the ascending aorta was followed by a similar monophasic hypotension with some time lag. Superposition of the both trancings suggested that the biphasic hypotension by the intravenous injection could be separately considered in the following manner; the first fall of hypotension was caused by the direct cardiac action through the coronary artery, and the second was produced by the peripheral action (Fig. 7). This concept differs from that of Muirhead in the interpretation of the biphasic hypotension. He considered the second fall to be caused by the coronary action of the saline. But its commencement was about 15 to 20 sec. after the injection and this interval was too long for the solution to reach the coronary beds through the pulmonary circulation.

ST and T abnormalities also appeared immediately after the injection and almost simultaneously with the systemic hypotension. Our observation demonstrated that the nearer the site of injection was to the coronary ostium, the earlier the ST and T changes appeared. For this reason, the ST and T changes might be considered to be a proof of arrival of the hypertonic saline at the coronary circulation.

Now, one problem is presented, and that is whether the ST and T changes are produced by the coronary ischemia or by the electrolyte imbalance. Using the perfused preparations, Read[9] observed the coronary resistance to decrease in parallel with the aortic resistance. Under the condition of constant flow, the decreased resistance was a reflection of the systemic hypotension, and so the true behavior of the coronary artery was not known. The original work of Muirhead[2] did not measure the coronary blood flow, although Walcott[17] cited the results as coronary constrictive effect. Katz and Lindner[18] showed the coronary dilator action of the Na ion in Langendorf's preparation, but the concentration of the solution and the rate of injection were not clearly mentioned. We also did not measure the coronary blood flow and no definite conclusion could be drawn concerning the dilator or constrictive action of the hypertonic saline to the coronary artery.

Electrocardiographic effects due to hypertonic saline are not fully understood. Scherf[19),20)] studied the impulse formation by the focal application of hypertonic saline and Eliakim[21)] extensively analyzed the ECG changes induced by intravenous injection of hypertonic saline but did not compare the differences due to the sites of injection. He observed the beginning of the ST and T changes to be 15 sec. after the injection, which was slightly longer than that of our experience. Prinzmetal and his associates[22)] analyzed a chemical origin of ST deviation, using the focal application and intracoronary injection of the sodium and potassium solution of varying concentrations. In nonischemic condition, a rapid injection of 5 ml. of hypertonic (even 0.9 to 1.1 per cent) saline into the artificial coronary artery circuit resulted in an immediate ST segment depression. This change progressively became more marked for 15 to 20 seconds, then on reaching its nadir gradually returned to the isoelectric line during the next 10 seconds to 2 or 3 minutes. They also observed a similar ST change in an injection of hypotonic potassium solution and explained that ST depression was related largely to the increase in ionic gradients of both potassium and sodium. According to this concept, ST depression can be explained even in the absence of myocardial ischemia.

From the above discussions, ST and T changes may be explained by the electrolyte imbalance due to hypertonic saline. However, marked hypotension produced simultaneously with or slightly later than ST and T changes can not be explained sufficiently by the electrolyte imbalance alone. On this account, any transient myocardial failure due to coronary ischemia must be considered besides the electrolyte imbalance.

As for the diminished P-waves and changes in amplitude of R deflection, the explication of their mechanism by the information of transmembrane potential and epicardial leads is still within the stage of speculation, since our results are obtained from a single limb lead.

In our experiments, injections were also made into the varying sites of the aorta for the purpose of comparison with effects of intravenous and intracardiac injection. Recently a number of papers have been presented about the peripheral action of hypertonic saline,[23)–27)] and our experiments are in progress in an attempt to add further information.

Summary

In order to clarify the mechanism of the triad, namely apnea, bradycardia and systemic arterial hypotension, produced after the intravenous injection of hypertonic saline, intracoronary injection technique, transeptal left atrial puncture and electrocardiographic analysis were applied in a total of 25 anesthetized closed-chest dogs.

(1) Bradycardia and apnea were demonstrated by the injection of

hypertonic saline into the inferior vena cava and pulmonary artery, but not into the left heart. Vagotomy eliminated both reactions completely. These were considered to be due to the pulmonary reflex via the vagus.

(2) Systemic hypotension had 2 dips after the injection into the right or left cardiac chamber, but after the injection into the coronary artery there was only one early dip. Injection into the distal part of the aorta also resulted in a monophasic hypotension, and its appearance was later than in the case of intracoronary injection. These 2 different kinds of monophasic dips corresponded in time and magnitude approximately to the 2 dips after the intracardiac injection. In about one-half of experiments, pulmonary hypertension occurred, and simultaneous decrease in left atrial pressure was found in only 6 of 91 experiments.

(3) In electrocardiograms, ST-segment and T-wave changes were shown to occur proportionally earlier as the site of injection approached nearer to the coronary ostium; immediately after the intracoronary injection and several seconds after the intravenous and intrapulmonary arterial injection. These changes were almost simultaneous with the first dip of hypotension.

(4) From above findings the authors emphasized the possibility that the initial dip of the arterial hypotension after the intravenous injection of the hypertonic saline was produced by the transient myocardial failure due to any myocardial ischemia and electrolyte imbalance. The mechanism of the second dip of the hypotension remained unsolved.

Acknowledgements

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Studies of Electrocardiographic Patterns in Cases with Neurosurgical Lesions

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Recent studies on the electrocardiographic patterns in cases with cerebrovascular accidents have shown that a neural factor might be responsible for the abnormalities in the electrocardiograms, but we have as yet very little clinical information in cases with neurosurgical lesions. The purposes of this presentation are to describe the pre- and postoperative electrocardiographic patterns and to discuss the possible causes inducing abnormalities in the postoperative electrocardiograms.

Evidence is presented in 323 neurosurgical cases that the high incidence of abnormal electrocardiographic patterns, especially flat or inverted T waves and S-T segments depression, are exhibited postoperatively in cases with supratentorial lesions, especially with craniopharyngioma, hypophyseal adenoma and other sellar tumors and with the fronto-temporal lobe tumors.

From the results of this study, it may be suggested that in cases with neurosurgical lesions, electrocardiograms may also be affected by a neural factor from surgical damage to the parapituitary areas of the central nervous system.

IN our previous paper,[1] various factors such as age, cardiovascular impairment (hypertension, arteriosclerosis, enlargement of the heart etc.), impaired liver function, electrolytes imbalance etc., have been considered as causing postoperative abnormalities in electrocardiograms. Apart from these, the site of the operation should also be considered as another additional causal factor.

Recent studies on electrocardiographic patterns in cases with cerebral trauma,[2)-5)] cerebrovascular accidents[6)-11)] or with pneumoencephalography[12)-18)] have shown both cerebral and cardiac findings on many occasions, and suggested that a neural factor might be responsible for the abnormality in the electrocardiograms. However, during the past couple of decades electrocardiographic patterns have rarely been observed in cases with brain tumors. Aschenbrenner and Bodechtel[19)] reported that, in electrocardiograms in younger patients with brain tumors, premature beats,

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abnormal T waves and S-T segments, etc. were disclosed frequently after brain surgery. In Bartelheimer's paper,[20] electrocardiograms revealed arrhythmias and S-T segments depression in most of the cases with acromegaly.

But, we have as yet very little clinical information as to whether or not any special area in the brain is connected with the induction of the abnormalities in the electrocardiograms. Therefore, the purposes of this presentation are to describe the pre- and postoperative electrocardiographic patterns and to discuss the possible mechanisms of the development of abnormalities in the electrocardiograms in cases with neurosurgical lesions.

Material and Method

Three hundred and twenty-three cases with various neurosurgical lesions admitted to the Surgical Department of Tokyo University Hospital, between September, 1957 and March, 1960, comprise the materials of this study. The diagnosis was accepted only if proved by one or more of the following clinical and laboratory findings: the history and clinical course of the present illness, neurological examination, X-ray diagnosis, electroencephalograms, etc.: or at surgery, or even at autopsy. Electrocardiograms were taken frequently at the pre- and postoperative periods in each case.

Results

Preoperative electrocardiograms in cases with neurosurgical lesions.

The incidence of abnormal T waves (flat or inverted T waves), S-T

Table I. Incidence of Preoperative Abnormal Patterns in the Electrocardiograms

		Flat T waves	Inverted T waves	S–T segments depression	Prolonged Q–T interval	Extrasystole	Miscellaneous
1) Supratentorial tumors (except 2)	(109 cases)	2.8%	1.8%	2.8%	5.5%		1.8%
2) Craniopharyngioma, hypophyseal adenoma and other sellar tumors	(56 cases)	5.4%	3.6%	1.8%	3.6%	3.6%	3.6%
3) Infratentorial tumors	(76 cases)	3.9%	1.3%	5.3%	2.6%		
4) Spinal cord tumors	(23 cases)			3.9%		3.9%	3.9%
5) Intracranial vascular anomaly	(15 cases)		6.7%	13.3%			6.7%
6) Depressed fracture of the skull	(15 cases)						6.7%
7) Intracranial hematoma	(16 cases)	6.3%					6.3%
8) Head injury	(13 cases)		7.7%	7.7%	7.7%	7.7%	7.7%

segments depression, Q-T interval prolongation and premature beats in the electrocardiograms checked before the surgery differed among different kinds of lesions (Table I).

Abnormal patterns of electrocardiograms, such as flat or inverted T waves, S-T segments depression, Q-T interval prolongation and premature beats were of the highest incidence in cases with head injury followed by cases with lesions at the sellar region, intracranial vascular anomaly, supratentorial tumors, infratentorial tumors, spinal cord tumors and chronic intracranial hematoma in that order of decreasing incidences. In our previous paper,[1] it was shown, that there was a significant difference in the incidence of abnormal electrocardiograms among various age groups in cases of general surgery—the older the patient, the higher the incidence of abnormal patterns. Although our cases with neurosurgical lesions consisted of rather younger-aged patients, it appeared obvious that there was a little difference of preoperative abnormal electrocardiograms between neurosurgical and general surgical cases even in the same age groups (Table II).

Table II. Incidence of Preoperative Abnormal T Waves and S-T Segments Depression in Various Age-brackets of Cases with Gastric Pathology (Gastric Cancer and Ulcer) and with Neurosurgical Lesions

a. Cases with gastric pathology

Age	0–29 (34 cases)	30–39 (43 cases)	40–49 (48 cases)	50–59 (94 cases)	60–69 (74 cases)	70– (17 cases)
1–Flat T waves or slight depression of S–T segments (below 0.1 mV.)		2.3%	2.1%	3.3%	8.4%	11.7%
2–Inverted T waves or marked depression of S–T segments (over 0.1 mV.)		2.3%	2.1%	2.1%	1.1%	
Total		4.6%	4.2%	5.4%	9.5%	11.7%

b. Cases with neurosurgical lesions (including various kinds of lesions)

Age	0–29 (100 cases)	30–39 (52 cases)	40–49 (90 cases)	50–59 (56 cases)	60– (25 cases)
1–Flat T waves or slight depression of S–T segments	6.5%	9.3%	5.5%	3.5%	10.7%
2 Inverted T waves or marked depression of S–T segments	0.9%	1.8%		7.0%	3.6%
Total	7.4%	11.1%	5.5%	10.5%	14.3%

Postoperative electrocardiograms in cases with neurosurgical lesions.

In these cases, various kinds of neurosurgical operations were performed under endotracheal anaesthesia with Nitrous-oxide-Oxygen- Barbiturate-

S.C.C. and serial electrocardiograms were recorded during and after the operation. The data, obtained at postoperative periods, is as seen in Table III. It is evident that high incidence of flat or inverted T waves,

Table III. Incidence of Abnormal Electrocardiographic Patterns Induced Postoperatively (in Cases with Preoperative Normal Electrocardiograms)

		Abnormal P waves	Flat T waves	Inverted T waves	S-T segments depression	Q-T interval prolongation	Extrasystoles
1) Supratentorial tumors (except 2)	(67 cases)	2%	21%	12%	6%	19%	2%
2) Craniopharyngioma, hypophyseal adenoma and other sellar tumors	(46 cases)	5%	41%	15%	16%	35%	5%
3) Infratentorial tumors	(47 cases)	8%	17%	4%	2%	11%	
4) Spinal cord tumors	(9 cases)		11%			22%	11%
5) Intracranial vascular anomaly	(8 cases)		12%		12%	12%	
6) Depressed fracture of the skull	(11 cases)	9%	18%			9%	
7) Intracranial hematoma	(15 cases)	7%		13%	13%	7%	

depressed S-T segments and prolonged Q-T interval in cases with tumors at the sellar region and with supratentorial tumors, was found even in cases with essentially normal preoperative electrocardiograms. It would be interesting to elucidate at what special sites of the central nervous system that an extremely high incidence of abnormal electrocardiograms was induced postoperatively, by the analysis of more precise anatomical sites of lesions (Table IV). The incidence of abnormal S-T segments and T waves was 85% in 13 cases with craniopharyngioma, 67% in 24 cases with hypophyseal adenoma, 67% in 9 cases with other kinds of tumors at the sellar region, 62% in 13 cases with temporal lobe tumors and 48% in 23 cases with frontal lobe tumors, but was rather low in cases with parieto-occipital lobe tumors and those with infratentorial lesions. In cases with craniopharyngiomas, hypophyseal adenoma and other sellar tumors, most of the abnormalities consisted of flat and inverted T waves, but the incidence of S-T segments depression was also markedly higher than in cases with infratentorial tumors. Therefore, it seemed likely that the sellar and temporo-frontal regions were the sites most predisposed in inducing the

Table IV. Incidences of Abnormal T Waves and S-T Segments Depression and of Prolonged Q-T Intervals (in Cases with Preoperative Normal Electrocardiograms)

		Flat T waves	Inverted T waves	S-T segments depression	Total	Prolonged Q-T intervals
1) Craniopharyngioma	(13 cases)	54%	23%	8%	85%	31%
2) Hypophyseal adenoma	(24 cases)	37%	8%	21%	67%	33%
3) Other sellar tumors	(9 cases)	34%	22%	11%	67%	45%
4) Temporal lobe tumors	(13 cases)	38%	15%	8%	62%	15%
5) Frontal lobe tumors	(23 cases)	17%	13%	17%	48%	33%
6) Parieto-occipital lobe tumors	(32 cases)	19%	9%		28%	9%
7) Infratentorial lesions	(47 cases)	17%	4%	2%	24%	11%
Gastric cancer and ulcer	(302 cases)	4%	2%	8%	15%	23%

Table V. Incidences of Postoperatively Induced Abnormal T Waves and S-T Segments Depression in Various Age-brackets of Cases with Gastric Pathology (Gastric Cancer and Ulcer) and with Neurosurgical Lesions (in Cases with Preoperative Normal Electrocardiograms)

a. Cases with gastric pathology

Age	0–29 (34 cases)	30–39 (41 cases)	40–49 (45 cases)	50–59 (88 cases)	60–69 (64 cases)	70– (15 cases)
1–Flat T waves or slight depression of S–T segments (below 0.1 mV.)	3.0%	2.4%	8.9%	7.9%	9.4%	33.3%
2–Inverted T waves or marked depression of S–T segments (over 0.1 mV.)	3.0%	2.4%	2.2%	3.4%	3.1%	6.6%
Total	6.0%	4.8%	11.1%	11.3%	12.5%	39.6%

b. Cases with neurosurgical lesions (including various kinds of lesions)

Age	0–29 (20 cases)	30–39 (18 cases)	40–49 (29 cases)	50–59 (16 cases)	60–69 (9 cases)
1–Flat T waves or slight depression of S–T segments (below 0.1 mV.)	15.0%	16.7%	34.5%	31.3%	22.2%
2–Inverted T waves or marked depression of S–T segments (over 0.1 mV.)	10.0%	5.6%	3.5%	12.5%	
Total	25.0%	23.3%	28.0%	43.8%	22.2%

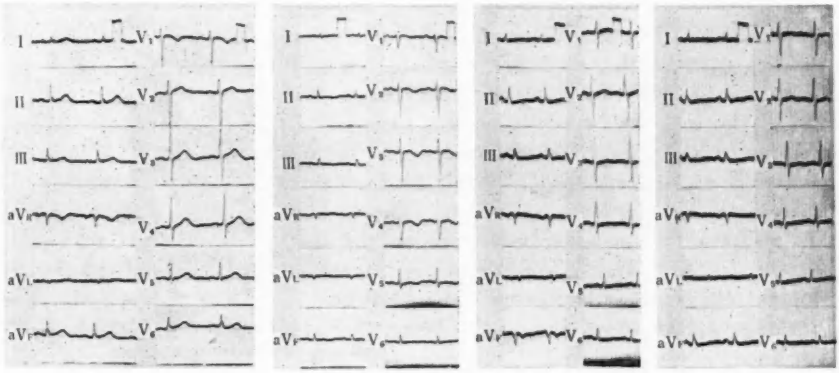
abnormal T waves and S-T segments postoperatively. On the other hand, no considerable difference could be found in the incidence of postoperatively induced abnormal S-T segments and T waves between cases with 2 kinds of tumors—meningioma and glioma.

As shown in Table V, these results apparently indicated that a marked difference in postoperative incidence of abnormal S-T segments and T waves was found between cases with gastric pathology and with these neurosurgical lesions, and that the incidence of postoperative electrocardiographic abnormalities in cases of each age group with neurosurgical lesions was approximately equal to the incidence in cases with gastric pathology even when the latter group belonged to an age-bracket that was over 30 years older.

Illustration of cases with abnormal electrocardiographic patterns induced after operation

Case 1. K. T. 35-year-old male. Craniopharyngioma.

The patient was admitted to the hospital because of craniopharyngioma with hypopituitarism. Left visual acuity has been impaired since 6 year of age, and episodes of nausea, vomiting and unconsciousness occurred occasionally since he was 10 years old. A large calcified tumor was found at the base of the frontal lobes and the suprasellar region both in plain craniograms and cerebral arterio-



A. B. C. D.

Fig. 1. K. T. 35-year-old male with craniopharyngioma.

A. Preoperative electrocardiograms showed no abnormal patterns.

B. Partial removal of the tumor was done by left frontal approach under general anesthesia. Electrocardiograms revealed flat T waves in leads I, aV_L, V_6, and inverted T waves in leads II, III, aV_F, V_{2-5} immediately after operation. Blood pressure was 100/80.

C. and D. Electrocardiograms still showed flat T waves in leads I, II, III, aV_L, aV_F, V_{4-6} on the first and eleventh postoperative days. Blood pressure was 120/85 and plasma K was 4.9 mEq./L. on the eleventh postoperative day.

grams. Other physical and laboratory examinations revealed dwarfism, hypoplasia of the sexual organ, mental retardation and psychomotor seizures. Investigations also showed a cerebrospinal fluid pressure of 100 mm. in water, low excretion of 17-O. H. C. S., total plasma cholesterol of 154 mg., serum potassium of 4.1 mEq./L., phenolsulfonphthalein excretion of 65% in 2 hours, protein-bound-iodine of 3.7γ/100 ml. and normal type of Mecholyl test. Blood pressure was 98/64 and no cardiac enlargement was revealed in the chest skiagram. Preoperative electrocardiograms were within normal limits, as shown in Fig. 1. Partial removal of the tumor was made by the left frontal approach under general anaesthesia with premedication of 10 mg. of atropine sulfate. The patient stood the operative procedure of one hour and 45 minutes quite well. Electrocardiograms recorded immediately after the operation, revealed flat T waves in all leads. Similar electrocardiograms of low to flat T waves were sustained without any symptom and sign of impaired cardiovascular function for about 2 weeks after the operation, although moderate elevation of body temperature occurred for about 20 days postoperatively.

In our previous paper,[1] it was shown in cases with general surgical diseases that abnormal T waves or depressed S-T segments immediately after the operation were less evident when the operation was done under general anaesthesia. In contrast, neurosurgical cases exhibited a higher incidence of abnormal patterns (81% in cases with craniopharyngioma, 67% in cases with hypophyseal adenoma and 57% in cases with other sellar tumors).

Except in a couple of cases showing slight decrease of T/R ratio, S-T segments and T waves were usually not changed during the operation even in cases with craniopharyngioma or with hypophyseal adenoma, although the Q-T interval was prolonged above the normal range in most of the serial electrocardiograms recorded during the operation. But, in a case with hypophyseal adenoma, the T waves in leads II and V_4 revealed a strong tendency of being biphasic when the operative procedure approached the hypophyseal region. The fact, that abnormal T waves or S-T segments were not found during the operation even in cases with postoperatively induced abnormal electrocardiograms, might be due to sufficient oxygen supply during the operation.

Other abnormal electrocardiographic patterns found postoperatively in some cases, were as follows:

Case 2. A. I. 20-year-old male. Posttraumatic epilepsy.

The patient had a skull fracture at the right parietal region at the age of 5, and sustained left spastic hemiplegia. He suffered attacks of generalized convulsive seizures since 10 years of age. At 16 years of age, cranioplasty was done at a hospital, but convulsive seizures could not be controlled by the medication. The patient was admitted to the hospital for right hemispherectomy. Physical examinations revealed left sided spastic hemiplegia, repeated generalized convulsive seizures, mental retardation, a blood pressure of 130/80 and no evidence of cardiovascular impairment. Right hemispherectomy was performed under general anaesthesia. Moderate fever and impaired consciousness occurred during the first

several postoperative days, but the patient was allowed to stand and walk 3 weeks after the operation. Preoperative electrocardiograms were within normal limits, but bursts of short P-Q intervals with abnormal QRS complexes were revealed in all leads thereafter when the right cerebral artery was ligated, and sustained until 6 hours after the conclusion of the operation. There was S-T segments depression during the first several postoperative days (Fig. 2).

Case 3. T. T. 32-year-old female. Hypophyseal adenoma.

The patient had noticed amenorrhea for the past 4 years, and had impairment of left visual acuity since 3 years ago. Physical examinations revealed left optic nerve atrophy with temporal hemianopsia, cerebrospinal fluid pressure of 180 mm. in water and a blood pressure of 110/72. No cardiovascular impairment was observed. Preoperative electrocardiograms were essentially normal. After subcapsular removal of the adenoma, moderate fever, nuchal rigidity and leucocytosis developed for the 10 postoperative days. Electrocardiograms of the first postopera-

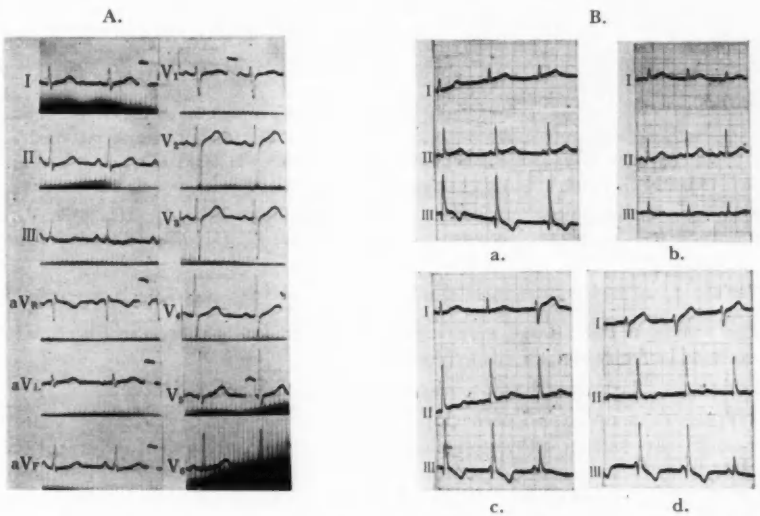
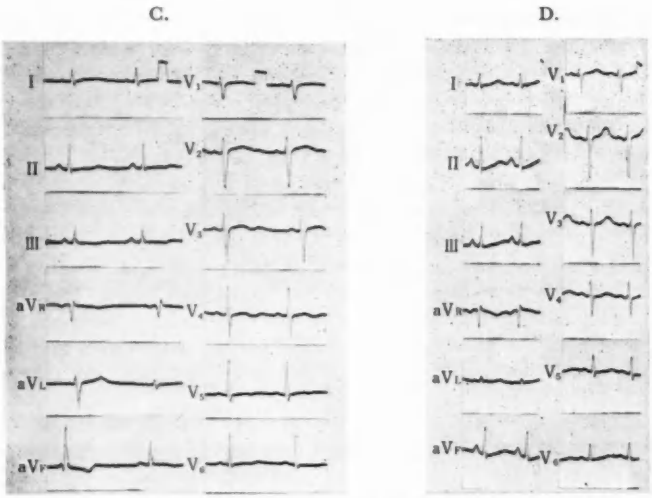


Fig. 2. A. T. 21-year-old male. Posttraumatic epilepsy and left sided spastic hemiplegia with mental retardation.

A. Preoperatively, electrocardiograms were within normal limits, except P waves of 0.3 mV. in standard and extremity leads. Blood pressure was 130/80.

B. Right hemispherectomy was done under general anesthesia. On serial electrocardiograms recorded during the operation, bursts of different amplitude and height of QRS complexes with accelerating A-V conduction occurred occasionally in association with a regular sinus rhythm thereafter when right anterior cerebral artery was tied (a—d).
a. Right internal carotid artery tied. B. P. 130/94 b. Right anterior cerebral artery tied. B. P. 122/94 c. Brain tissuses near the basal ganglion resected. B. P. 130/88 d. Right occipital lobe manipulated. B. P. 122/82



C. The abnormal patterns of P–Q intervals and QRS complexes sustained until about six hours after the conclusion of the operation. Electrocardiograms recorded six hours after operation, revealed low-to-flat T waves in leads I, II, aV_L, V_{1-6} and slightly inverted T waves in leads III, aV_F. Blood pressure was 120/58.

D. On the first postoperative day, T waves were low in leads II, III, aV_F, V_{4-6}, and S–T segments depression appeared in leads II, III, aV_F. Blood pressure was 120/70.

tive day revealed multifocal, ventricular premature beats as seen in Fig. 3, withou any evidence of circulatory disturbance.

Case 4. Y. Y. 41-year-old male. Recurrent hypophyseal adenoma.

The previous operation of hypophyseal adenoma was performed 3 years ago, but recently the patient exhibited clinical symptoms and signs of recurrent tumor. Physical examinations revealed optic nerve atrophy with bitemporal hemianopsia, cerebrospinal fluid pressure of 150 mm. in water, blood pressure of 84/60 and no cardiac enlargement. Preoperative electrocardiograms disclosed the incomplete right bundle branch block (Fig. 4). Subcapsular, partial removal of the tumor was made through the frontal route under general anaesthesia. After the conclusion of craniotomy, the general condition deteriorated. Blood pressure rose to 158/106 and the patient showed drowsiness, anisocoria and hyperthermia. About 17 hours after the first operation, re-exploration of the right frontal and hypophyseal regions revealed a small epidural haematoma with a small-sized blood clot in the region of the anterior clinoid process and oozing from the tumor tissue. After the second operation, the patient's status remained unchanged, and respiration was assisted. Twenty-two hours after the first operation, blood pressure became 70/60 and body temperature was elevated to 42°C. Electrocardiograms during this period revealed sinus tachycardia with complete right bundle branch block, showing more serious impairment of intraventricular conduction system. The

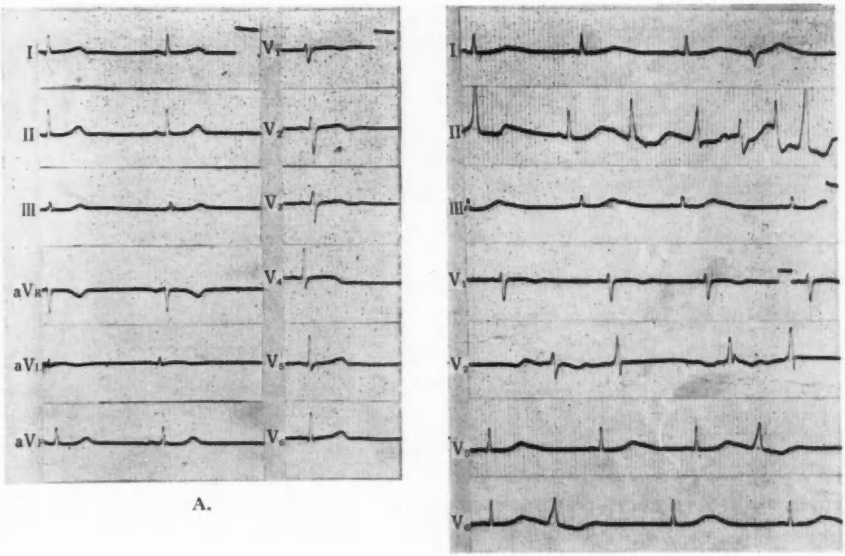


Fig. 3. T.T. 32-year-old female with hypophyseal adenoma.

A. Preoperative electrocardiograms showed sinus bradycardia with normal QRS complexes, S-T segments and T waves. Blood pressure was 110/72.

B. Left frontal craniotomy and subcapsular removal of the adenoma were done under general anesthesia. On the first postoperative day, multifocal, ventricular premature beats were seen in association with a regular sinus rhythm, and blood pressure was 124/90.

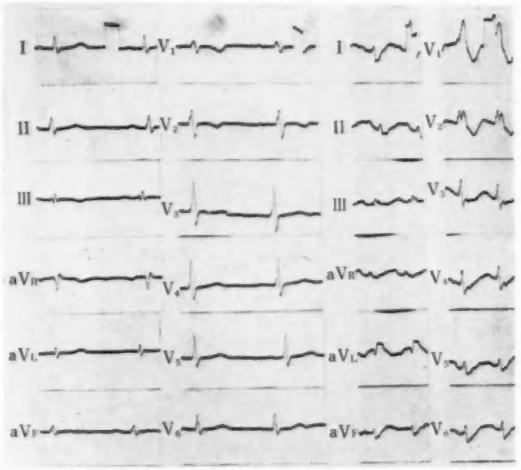
patient died 2 hours later, and autopsy revealed large hypophyseal adenoma compressing the ventral portion of the pons.

It is of interest to know that a high incidence of abnormal electrocardiographic patterns occurred postoperatively in cases with neurosurgical lesions, but when discussing the correlation between brain surgery and postoperative abnormal electrocardiograms, we should bear in mind that the changes in the postoperative electrocardiograms might be due to some functional mechanism.

Most cases with cerebrovascular accidents were associated with impairment of coronary artery and myocardium, and, therefore, there were many occasions where it was very difficult to obtain any information as to whether or not there was any relation between brain damage itself and electrocardiographic abnormalities.

We could find just the same situation in neurosurgical cases as in the cases with cerebrovascular accidents.

Case 5. T. T. 51-year-old male. Subarachnoid hemorrhage.



A. B.

Fig. 4. Y. Y. 41-year-old male with recurrent hypophyseal adenoma.

A. Preoperative electrocardiograms disclosed slightly wide QRS complexes in standard and extremity leads and atypical late R in V_{1-2}.

B. On the first postoperative day when general condition had deteriorated, electrocardiograms revealed sinus tachycardia with complete right bundle branch block in association with flat T waves. Blood pressure was 80/50.

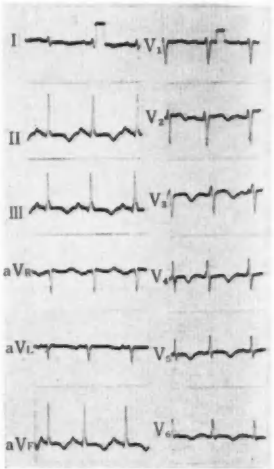


Fig. 5. T. T. 51-year-old male with subarachnoid hemorrhage due to a ruptured aneurysm of anterior communicating artery.

On the second day of admission, electrocardiographic prtterns revealed sinus tachycardia with inverted T waves in leads I, II, III, aV_F, V_{2-6}. P waves were shown over 0.3 mV. in standard leads.

Fifteen days before the admission to the surgical department, the patient was drunk and fell against a corner of a desk, with resultant unconsciousness for about one hour. Six days later, the patient complained of severe occipital headache and his consciousness was impaired. On the day of the admission, physical examination revealed delirium, signs of meningeal irritation, tonic neck reflex, choked discs, facial palsy and loss of superficial reflexes on the left side. Blood pressure of 130/100, and blood-stained cerebrospinal fluid with increased pressure of 350 mm. in water. Repeated examinations of electrocardiograms revealed sinus tachycardia with inverted T waves (in leads I, II, III, aV_F and V_{2-6}) and S-T segments depession (in lead II, III and aV_F), as shown in Fig. 5. The patient's condition over the next 4 days deteriorated gradually with corresponding changes in symptoms and physical signs, complicated with bronchopneumonia. He succumbed to the ailment on the fifth day. Autopsy revealed subarachnoid hemorrhage caused by a ruptured aneurysm at the site of the anterior communicating artery, marked swelling of the brain tissue and high grade sclerosis of the basilar artery. On the other hand, there were concentric hypertrophy of bilateral ventricles of the heart with diffuse subendocardial hemorrhage in the myocardium of the left ventricle, and with moderate sclerosis of left coronary artery, hemorrhagic bron-

chopneumonia of bilateral lower lobes and arteriosclerotic kidneys.

This case demonstrated the difficulties in determining whether or not such an organic change as diffuse subendocardial hemorrhage was associated frequently with brain surgery and whether or not the abnormal electrocardiograms were traced by the postoperatively induced organic changes of the myocardium. Therefore, we must be meticulous in our consideration of any relationship between brain surgery and electrocardiograms.

Discussion

As described above, Aschenbrenner and Bodechtel[19] reported, over 20 years ago, on several young patients that abnormal electrocardiograms were frequently observed after brain surgery. Our findings in 323 cases with neurosurgical lesions were essentially similar to those of Aschenbrenner and Bodechtel, and furthermore, we noted with great interest that abnormal electrocardiographic patterns were most frequently observed after operations in the sellar region (in cases with craniopharyngioma, hypophyseal adenoma and other sellar tumors). The exact mechanism which induces abnormal electrocardiograms frequently after brain surgery has been poorly understood, but 2 factors might be regarded as the principal causes:

1) Influences caused by general surgical stress:

Various operative procedures, acting as a general stressor, might cause such impairments as hypotension, hyper-or hypopotassemia, hypoxia, hypercapnea, anemia, impaired liver function and so on. Each of these might possibly influence the postoperative electrocardiographic patterns even in cases with neurosurgical lesions. Therefore, various kinds of clinical and laboratory findings were carefully examined to obtain any information about the causal factor inducing postoperative abnormal electrocardiograms.

a) Age: The average age of these neurosurgical cases was rather young, and there was no definite difference in the incidence of abnormal S-T segments and T waves among the various age groups for cranio-

Table VI. Incidences of Abnormal T Waves and S-T Segments Depression Postoperatively Induced in Cases with Craniopharyngioma, Hypophyseal Adenoma and Other Sellar Tumors

Age		Incidence of abnormal patterns	Age		Incidence of abnormal patterns
0–9	(1 case)	100%	40–49	(14 cases)	64.3%
10–19	(8 cases)	87.5%	50–59	(7 cases)	71.4%
20–29	(7 cases)	71.4%	over 60	(2 cases)	100%
30–39	(7 cases)	57.1%			

pharyngioma, hypophyseal adenoma and other sellar tumors (Table VI). Therefore, age could not be considered as one of the main causal factors which induced postoperative abnormal electrocardiograms frequently in cases with neurosurgical lesions.

b) Coexistence of cardiovascular disorders (hypertension, arteriosclerosis and so on): In our previous paper,[1] it was shown that postoperative abnormal electrocardiograms might be induced much more frequently in cases associated with hypertension or with arteriosclerosis than in the control group, but this was not found in most of cases with craniopharyngioma, hypophyseal adenoma and other sellar tumors.

c) Fluctuation of blood pressure during operation and at the postoperative period: Even during long operative periods in the supine position and during the postoperative periods, the blood pressure remained at a constant level in most cases with craniopharyngioma, hypophyseal adenoma and other sellar tumors, which induced high incidence of abnormal electrocardiograms postoperatively. On the other hand, in cases with infratentorial tumors, operations were performed with the patient in the face-down position. In this position, it was rather more difficult to maintain general circulation in a normal range than in a supine position, but the incidence of inducing abnormal patterns, except sinus tachycardia, on the electrocardiograms was much lower than in cases with other lesions.

It is unreasonable to suppose that the high indicidence of abnormal electrocardiograms is usually caused by any fluctuation of the blood pressure in cases with neurosurgical lesions.

d) Electrolyte balance: It might be possibly considered that impaired balance of electrolytes could be induced after causing the surgical stress to the hypophysis-hypothalamic region, but in our cases, there was no evidence to support this possibility, at least, from the standpoint of the incidence of hypopotassemia.[21] Postoperative hypopotassemia occurred frequently in general surgical cases when postoperative parenteral administration of potassium-deficient fluid was continued for long periods, but in neurosurgical cases, most patients could take food by mouth or by nasal tubing from the early postoperative days, and therefore, it could be supposed that, in general, most neurosurgical patients did not exhibit marked hypopotassemia or potassium deficiency.

e) Postoperative anaemia: It was our coworker, Yokoyama,[21] who stressed the high incidence of postoperative anaemia in neurosurgical patients who had operations in the supratentorial region, especially the base of the brain. But, when considering that it was rather rare to find abnormal S-T segments and flat or inverted T waves in chronic anaemia or even in the stage of acute anaemia due to gastric hemorrhage in younger patients, postoperative anaemia in neurosurgical cases could not be considered as a causal factor of abnormal electrocardiograms.

f) Increased intracranial pressure: Incidence of postoperative abnormalities in the electrocardiograms was low in cases with infratentorial tumors associated with increased intracranial pressure, and on the other hand, it was markedly high in cases with craniopharyngioma and hypophyseal adenoma without any evidence of postoperative rise in intracranial pressure. Therefore, increased intracranial pressure itself could not be considered as an important factor.

g) Hypoxia: During the postoperative period, pO_2 in blood was slightly reduced and pCO_2 was slightly elevated even for a short duration in some of the neurosurgical cases just as in general surgical cases. In a case with subdural hematoma, a 69-year-old male, preoperative electrocardiograms were within normal limits, but inverted T waves with sinus tachycardia were seen in postoperative electrocardiograms. As the patient was comatose on the third postoperative day, the second exploration was made under endotracheal oxygen supply with muscle relaxant. The postoperatively induced inverted T waves reverted to normal positive T waves with sinus tachycardia at the conclusion of the reexploration against postoperative epidural hematoma. We also found in many neurosurgical cases with long-duration of apnea whose respiration had to be assisted and electrocardiograms were within normal limits. These cases showed that postoperative hypoxia, due to various causes, influenced electrocardiographic patterns as frequently in the neurosurgical cases as in general surgical cases, although we tried, in each occasion, to administer sufficient oxygen by nasal catheter.

From the discussions mentioned in above, we could not find any definite and common factor among possible causes with an exception of hypoxia. Although each of these factors gave just a slight influence to the electrocardiographic patterns, they might be able to induce mass collective abnormalities on the electrocardiograms with the coexistence of several factors. Further attempts should be directed toward elucidating factors responsible for postoperative abnormal electrocardiograms.

2) Influences caused by neural factor:

As Wassermann[10] described in his paper on the induction of abnormal electrocardiograms associated with cerebrovascular accidents, various areas of the central nervous system might be affected both directly or indirectly after brain surgery. For example, the impairment of electrolytes and fluid balance could be induced by surgical damage of the brain, and then could affect the function of the heart indirectly.[10] On the other hand, the inhibitory and augmented center of the cardiovascular system lies in close proximity of the medulla oblongata in the floor of the fourth ventricle, and its highest center is found in the region of the hypothalamus and the frontotemporal and parietal lobes.[22]-[25] Therefore, surgical damage in close proximity to these areas, might also cause functional alterations of

the heart muscle or might affect cardiac rhythm directly. In 1922, Lennox, Graves and Levine[26] reported that abnormalities of the electrocardiograms were observed more frequently in cases with intracranial or cervical operations than in cases with operations on other areas, and that only the factors which might be concerned with alterations in vagal tone, seemed to be of importance in the induction of the abnormalities. We must then consider whether or not it was possible for cardiac function to be influenced through the neural pathway by direct surgical attack on the hypophyseal or hypothalamic region. There was evidence to support this idea in our series:

Firstly, most cases with operation on the hypophyseal region exhibited rather long R-R intervals both pre- and postoperatively, but many cases with lesions at other areas of the brain, especially at the infratentorial region, were generally associated with short R-R intervals during the early postoperative days. This result supported Takeuchi's clinical view[27] that

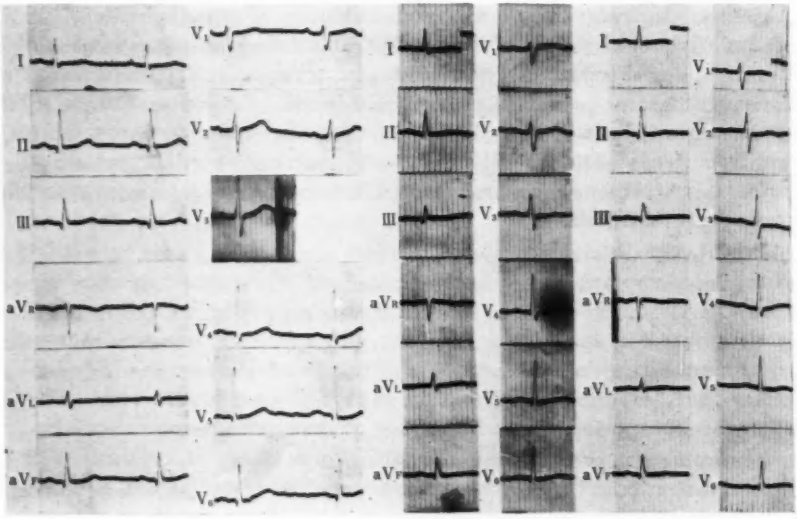
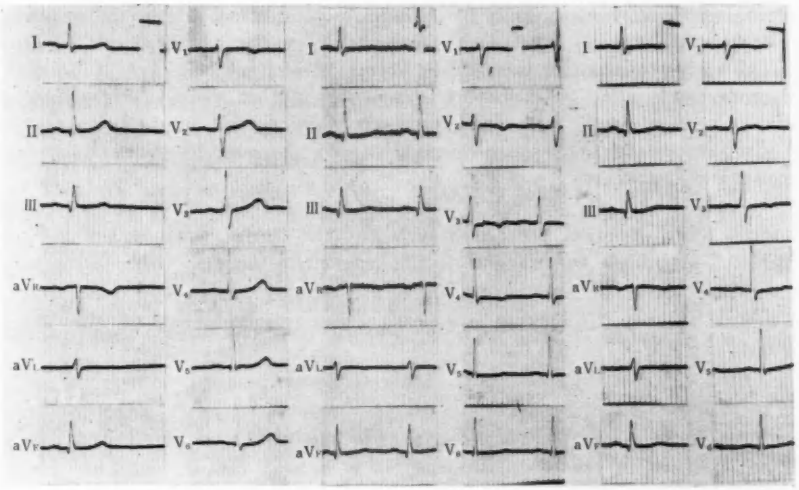


Fig. 6. K. I. 45-year-old male with craniopharyngioma.

A. Preoperative electrocardiograms were within normal limits. Laboratory findings showed blood pressure of 120/82, hematocrit of 40.9% and plasma K of 3.9 mEq./L. (July, 1959).

B. Left frontal craniotomy was done to remove the cyst. Electrocardiographic patterns were flat T waves in all leads on the first postoperative day. Blood pressure was 120/80.

C. Flat T waves still remained on the second postoperative day, when blood pressure was 118/78 with hematocrit of 36.0% and with plasma K of 4.2 mEq./L.



D. E. F.

D. Preoperative electrocardiograms were within normal limits on the day of re-admission when consciousness was impaired due to the recurrence of the tumor (February, 1960).

E. and F. The cyst of craniopharyngioma was aspirated with a needle through a small skin incision. On the first and second postoperative days, electrocardiograms revealed exactly the same flat T waves as at the previous operation. Blood pressure was 118/78–120/80 and serum K was 3.7 mEq./L. on the second postoperative day.

the elevation of the base of the frontal lobe with the brain spatula induced sinus bradycardia during the operation. Kamiya, Ohaku, Akiyama and Nakamura[28] reported that, although tachycardia and the lowering of peripheral digital plethysmograms were exhibited during brain surgery, bradycardia and the increase in the amplitude of plethysmograms were found occasionally when the surgical procedures involved the hypothalamic region.

These clinical findings might be supported by various experimental studies on circulatory changes caused by chemical or electrical stimulations of the hypothalamic region.[29)-32)]

Secondly, it was of considerable practical significance that similar electrocardiographic patterns were observed after 2 different operations on the same patient, as shown in Fig. 6.

Case 8. K. I. 45-year-old male with craniopharyngioma.

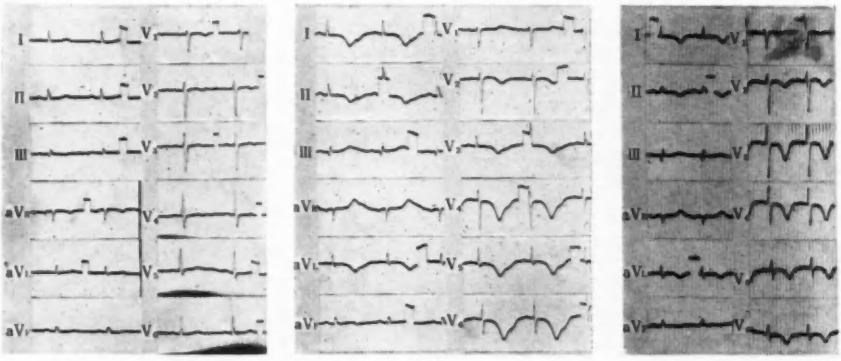
The first frontal craniotomy was done 3 years ago, and when the patient had the second craniotomy 9 months ago (July, 1959) to remove the recurrent craniopharyngioma electrocardiograms showed flattenning of T waves immediately after the operation and for the first postoperative day. The patient was re-admitted to

the surgical department because of impaired consciousness due to the recurrence of the tumor (February, 1960).

The electrocardiogram was within normal limits on the day of admission, but immediately after the operation when the cyst of craniopharyngioma was aspirated with a needle through a small skin incision, and on the first postoperative day, the electrocardiograms revealed exactly the same T waves change as at the previous operation.

It would be of interest to know that similar electrocardiographic patterns were induced postoperatively in the same patient on different occasions, although the nature of the operation varied. The result might show that some of electrocardiographic abnormalities could be induced by neural factors directly or indirectly from special areas of the central nervous system.

Thirdly, we could consider a special T waves pattern. Burch[9] described the so-called "large negative T waves" associated with cerebrovascular accidents as a new electrocardiographic pattern, and attributed this abnormal pattern of electrocardiogram to a neural factor. Similar electro-



A. B. C.

Fig. 7. N. T. 40-year-old female with metastatic cancer of left frontotemporal lobe.

A. Preoperative electrocardiograms showed low T waves in precordial leads. Blood pressure was 130/70. Physical and laboratory examinations showed a cerebrospinal fluid pressure of 280 mm. in water, hematocrit of 40.0%, plasma Na of 140 mEq./L., plasma K of 4.5 mEq./L. and plasma Cl of 101 mEq./L.

B. Left fronto-temporal decompression and biopsy of the tumor tissue were done under general anesthesia. On the first postoperative day, blood pressure was 120/70, but electrocardiograms revealed prolonged Q-T intervals and large negative T waves in leads I, II, aV_L, V_{3-6}. It was found that large negative T waves and U waves jointly gave rise to large negative waves.

C. Even on the eleventh postoperative day, the similar patterns were still found as on the first postoperative day. Blood pressure 124/80, plasma K 4.4 mEq./L., and no evidence of cardiovascular impairment.

cardiograms were observed in 3 cases with neurosurgical lesions (meningioma of the orbital surface, falx-meningioma and metastatic tumor of left fronto-temporal lobe), as illustrated in Fig. 7. The pattern of electrocardiograms consisted of prolonged Q-T interval and negative T waves of considerable amplitude and width, as described by some authors. In some cases, it was found that large negative T waves and U waves jointly gave rise to large negative waves. Although Levine,[83] Ippolito et al.,[84] Pruitt et al.,[85] Garcia-Palmieri et al.[86] and Goldman[87] reported that the large negative T waves were exhibited in cases with coronary heart disease and that an important factor was seemingly the existence of a coronary insult, we found that the peculiar patterns were not associated with any symptom and sign of evident cardiac and circulatory impairments. They were reverted to normal patterns when the clinical condition improved. We observed 3 other cases with large negative T waves induced after laparotmy and thoracotomy. It might be possible to consider the correlation between a neural factor, especially the vagal nerve, and the large negative T waves, as suggested by Burch,[9] but this subject needs further study.

From these various data, it may be suggested that the electrocardiographic patterns could also be affected by surgical damage to the special areas of the central nervous system directly through the neural pathways. However, further investigations are needed since these abnormal patterns might also be caused possibly by various impaired functions induced after brain surgery.

Summary

(1) Evidence has been presented in 323 neurosurgical cases that serial electrocardiograms exhibited high incidence of postoperative abnormal patterns in cases with intracranial surgical lesions, especially with tumors near the sellar region (craniopharyngioma, hypophyseal adenoma and other sellar tumors) and with the fronto-temporal lobe tumors. Most of the abnormalities in the electrocardiograms consisted of flat or inverted T waves and S-T segments depression, but the incidence of abnormal S-T segments was much less than that of abnormal T waves.

(2) The mechanism of inducing these phenomena has been briefly discussed. It has been suggested that electrocardiographic patterns might be affected by a neural factor after direct or indirect surgical damage to the parapituitary areas of the central nervous system.

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Algebraic Reflections on the Vector Concept in Electrocardiography

Part III. Representation of the Electric Field

Mitsumasa SATO, M.D.

Different from the previous 4 chapters dealing with one electric field, the present chapter concerns a set of the fields. The structure of the set of electric fields and its vectorial nature are discussed by refering to its "*homomorphic image*" or "*representation.*" Here the widely accepted method in practical electrocardiography, the "*mean spatial vector*" method, is criticized from this point of view.

This chapter may be summarized by a catchy expression *ELECTRIC FIELD IS VECTOR*, corresponding to the expression in Part I that *ELECTROCARDIOGRAM IS VECTOR.*

AFTER studying the structure of one electric field in previous report,[20] the set of fields must be analysed to clarify the relation between one and another electric fields or between the fields before and after some change of electromotive force of the heart. This chapter was prepared for this purpose.

Chapter 5.

HOMOMORPHIC IMAGE OF THE ELECTRIC FIELD

In this chapter, the set $\overline{\Pi}$ of the n-dimensional fields is analysed, where the body surface $\overline{\mathfrak{S}}$ is considered as the same.

p, p' and p'' are the potentials of a field-position s on $\overline{\mathfrak{S}}$ in respective three fields $\overline{\mathfrak{P}}$, $\overline{\mathfrak{P}}'$ and $\overline{\mathfrak{P}}''$ in $\overline{\Pi}$. When the relation $p=p'+p''$ holds for any s, $\overline{\mathfrak{P}}$ may be expressed as the sum of $\overline{\mathfrak{P}}'$ and $\overline{\mathfrak{P}}''$, and the addition will be defined in Π. ($\overline{\mathfrak{P}}=\overline{\mathfrak{P}}'+\overline{\mathfrak{P}}''$) Similarly, an external multiplication by F is defined in $\overline{\Pi}$, when $p=ap'$, $a\epsilon F$ holds for any s. ($\overline{\mathfrak{P}}=a\overline{\mathfrak{P}}'$) Then, $\overline{\Pi}$ is extended to Π, the set of all linear combinations of a finite number of fields in $\overline{\Pi}$. Π is more concretely impressed, when it is studied in connection with Π.

As $\mathfrak{P}\epsilon\Pi$ is the set of linear combinations of elements p^1, p^2,....., p^n corresponding to adequately selected basic field-positions[10] s^1, s^2,....., s^n on $\overline{\mathfrak{S}}$, the combination of these n-elements, $\overline{P}=\begin{pmatrix} p^1 \\ p^2 \\ \vdots \\ p^n \end{pmatrix}$,may represent $\overline{\mathfrak{P}}$. Set $\overline{\mathbf{P}}$ consisting of $\overline{P}$'s cor-

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responding to all the fields in Π is homomorphic to Π with regard to the addition and the external multiplication in $\overline{\mathbf{P}}$, when they are defined in the similar way as in Π. When the components $p^1, p^2, \ldots\ldots, p^n$ of $\bar{P}$ are mapped to $P^1, P^2, \ldots\ldots, P^n$ by means of mapping-π (Chapter 4), $\bar{P}=\begin{pmatrix} p^1 \\ p^2 \\ \vdots \\ p^n \end{pmatrix}$ is mapped to $P^*=\begin{pmatrix} P^1 \\ P^2 \\ \vdots \\ P^n \end{pmatrix}$. Set $\mathbf{P}^*$ consisting of P^*'s corresponding to all $\bar{P}$ in $\overline{\mathbf{P}}$ is homomorphic to $\overline{\mathbf{P}}$. And as $\overline{\mathbf{P}}$ is homomorphic to Π, $\mathbf{P}^*$ is homomorphic to Π. And as

$$P^*=\begin{pmatrix} P^1 \\ P^2 \\ \vdots \\ P^n \end{pmatrix}=\begin{pmatrix} p_1^1 p_2^1 \cdots\cdots\cdots p_n^1 \\ p_1^2 p_2^2 \cdots\cdots\cdots p_n^2 \\ \cdots\cdots\cdots\cdots\cdots \\ p_1^n p_2^n \cdots\cdots\cdots p_n^n \end{pmatrix}=(P) \qquad (5\text{–}1)$$

$\mathbf{P}^*$ is a linear algebra composed of $n\times n$ matrices.[1),4)] Hence,

1) The set of the equi-dimensional electric fields has a linear algebra composed of $n\times n$ matrices as its homomorphic image, where n is dimension-number of the fields.

2) The set of the fields has a finite-dimensional vector space as its homomorphic image.

3) The set of the field is represented by the algebra composed of $n\times n$ matrices. In the sense of 2), or in the homomorphic sense,

"*the electric field may be regarded as a vector.*" ELECTRIC FIELD IS VECTOR.

It was mentioned in Chapter 2 that an electrocardiogram recorded from a point on the body surface might be regarded as a vector. But the author found in the above 2) that the set of electrocardiograms recorded from all over the body surface, the electric field itself, might also be regarded as a vector in the homomorphic sense. In practical electrocardiography, the concept "mean spatial vector" has been widely used recently. The author's opinion about utility of this concept is that the mean spatial vector has been introduced in order to "*compare*" several fields with each other. Every field is represented by its own mean spatial vector, and comparison of the vectors representing the respective fields makes that of the fields possible. In this sense, a field may have been regarded as a vector. The results above-mentioned, 1), 2) and 3), correspond to this conventional view. But it is still unknown, how and to what degree the mean vector, integration of instant vector, could represent the field, and what relationship have the vectors, representing the fields, between each other. In order to solve these questions, the author is going to discuss generalizing the problem of representation of the field Π in this chapter.

The "representation" here is introduced for practical purposes and has somewhat different sense from that in algebra,[1),2)] although this concept covers the representation in algebra. There are a set $\boldsymbol{S}$ and another set $\boldsymbol{A}$ for which a law of composition ω is defined. When an element of $\boldsymbol{S}$ corresponds surely to one element of $\boldsymbol{A}$ by correspondence γ, it is called that "$\boldsymbol{S}$ is represented by γ in $\boldsymbol{A}$", that an element a of $\boldsymbol{A}$ corresponding to an element s of $\boldsymbol{S}$ is "representation of s by γ", that set $\boldsymbol{A}'$ consisting of a's corresponding to all s's of $\boldsymbol{S}$ is "representation

of $\boldsymbol{S}$ by γ", and that "γ is a representor of $\boldsymbol{S}$." Of course $\boldsymbol{A}' \subseteq \boldsymbol{A}$. When s_1, $s_2 \in \boldsymbol{S}$ and they have the same representation by γ, this relation is expressed as $s_1 \equiv s_2$ (γ) ,which is an equivalence relation[1),2)]. Then, a classification of $\boldsymbol{S}$ is possible by this relation. This is said as the "classification of $\boldsymbol{S}$ by its representation $\boldsymbol{A}'$". If $\boldsymbol{S}$ has two representations $\boldsymbol{A}_1$ and $\boldsymbol{A}_2$ in $\boldsymbol{A}$, and if $\boldsymbol{A}_2 \subset \boldsymbol{A}_2$ holds, the representation $\boldsymbol{A}_1$ is said "more strict" than $\boldsymbol{A}_2$. This is the concept that expresses to some extent the degree of fidelity of the representation.

When one intends to represent $\boldsymbol{S}$ in $\boldsymbol{A}$, $\boldsymbol{A}$ may be selected in many ways theoretically, but in practice $\boldsymbol{A}$ must have somewhat concrete significance according to the purposes. Moreover, the law of composition ω in $\boldsymbol{A}$ may be expected to have a concrete significance, because ω is the law of composition also in $\boldsymbol{S}$ when it is mapped homomorphically into $\boldsymbol{S}$, though $\boldsymbol{S}$ has originally no law of composition. If there are defined m-practically significant laws of composition in $\boldsymbol{A}$, $\boldsymbol{A}'$ is a "representation of m-degrees". The more strict is the representation, the more it is precise. And the higher is its degree, the more it is practically significant.

Here is a familiar example of representation. $\boldsymbol{S}$ is here a set of all the points on a two-dimensional plane (Fig. 4). From a point s in $\boldsymbol{S}$, perpendicular line is drawn to a line x, and its foot is signed as s_x. The set consisting of a_x's corresponding to all s's in $\boldsymbol{S}$ is F (the field of real numbers), where a_x is a distance from a fixed point O on x to s_x, measured by certain unit. Then, F is a representation of $\boldsymbol{S}$ or $\boldsymbol{S}$ is represented in F and by F $(F=\boldsymbol{A}_1)$. Representation a_x of point s signifies a sort of distance from O to s. When two laws of composition ω_1 and ω_2, are defined in $\boldsymbol{A}_1$ as $a_{1x}\omega_1 a_{2x} = a_{1x} - a_{2x}$, $a_{x1}\omega_2 a_{2x} = a_{1x}/a_{2x}$,they are significant. ω_1 signifies a sort of distance between two points s_1 and s_2, and ω_2 signifies a ratio of

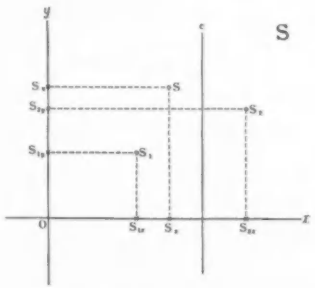

Fig. 1. An example of representation.

distances from O to s_1 *and* s_2. There may be thought all kinds of laws of composition other than ω_1 and ω_2, but they have lesser significance than ω_1 and ω_2, in the usual sense. Thus, $\boldsymbol{A}_1$ is a representation of two degrees.

A more strict representation of $\boldsymbol{S}$ than $\boldsymbol{A}_1$, shall be demonstrated as follows. A line $\boldsymbol{y}$, perpendicular to x, crosses x at O. s_y and a_y are determined in the same way as s_x and a_x. Set consisting of a_y's is F. If addition and multiplication are defined in $\boldsymbol{A}_2$, the set of ordered sets (a_x, a_y)'s of two real numbers a_x and a_y, as $(a_x, a_y)+(a'_x, a'_y)=(a_x+a'_x, a_y+a'_y)$, $(a_x, a_y)\cdot(a'_x, a'_y)=(a_x\cdot a'_x, a_y\cdot a'_y)$, $\boldsymbol{A}_2$ is also a field. Here, we have a representation of S by making the element (a_x, a_y) of $\boldsymbol{A}_2$ correspond to point s. Representation (a_x, a_y) of s signifies a sort of quantity which shows how the point s is distant from the point O. When two laws of

composition ω_1 and ω_2 are defined in $\boldsymbol{A}_2$ as $(a_{1x},a_{1y})\omega_1(a_{2x},a_{2y})=(a_{1x},a_{1y})-(a_{2x},a_{2y})$, $(a_{1x},a_{1y})\omega_2(a_{2x},a_{2y})=(a_{1x},a_{1y})\,/\,(a_{2x},a_{2y})$, they are also significant in almost the same meaning with ω_1 and ω_2 in $\boldsymbol{A}_1$. Thus, $\boldsymbol{A}_2$ is a representation of two degrees. And as obviously $\boldsymbol{A}_1 \subset \boldsymbol{A}_2$ holds, $\boldsymbol{A}_2$ is more strict than $\boldsymbol{A}_1$.

A class in the classification by $\boldsymbol{A}_1$ shows a straight line c, any point on which has the same representation in $\boldsymbol{A}_1$. And a class in the classification by $\boldsymbol{A}_2$ is a only one point. Hence, as to this example, there is no more strict representation than $\boldsymbol{A}_2$.

Π is represented in $\boldsymbol{P}^*$, and by $\boldsymbol{P}^*$. In this case, $\boldsymbol{P}^*$ is a representation in also algebraic meaning. The character and the meaning of the representation $\boldsymbol{P}^*$ of Π shall be discussed as follows. This will clarify the character and structure of Π and $\overline{\Pi}$.

When $\overline{\mathfrak{P}}$ and $\overline{\mathfrak{Q}}$ in $\overline{\Pi}$ have the same representation in $\boldsymbol{P}^*$ or $\overline{\mathfrak{P}}$ and $\overline{\mathfrak{Q}}$ are in the same class in the classification by $\boldsymbol{P}^*$, the bases P and Q of potentials p and q ($p \in \overline{\mathfrak{P}}$, $q \in \overline{\mathfrak{Q}}$) are expressed as $P=(P')A$, $Q=(Q')B$ from formula (2-13)''. As $(P)=(Q)$ here, or in other words, as the bases of the two fields are equal, $P=Q$ or $p_i=q_i$ $(i=1,2,\ldots\ldots,n)$ holds, if $A=B$, where $P=(p_1,p_2,\ldots\ldots,p_n)$, $Q=(q_1,q_2,\ldots\ldots,q_n)$. Hence, "*not only the bases of two electric fields in the same class, but also the bases of electrocardiograms of the respective fields are equal, if field-position-coordinates of the two electrocardiograms are equal*".

One of the laws of composition, ω_1, in $\boldsymbol{P}^*$ is defined as $Q^*\omega_1 P^*=Q^*/P^*=(QP^{-1})=(K)$ $|P|\neq 0$, where P^* and Q^* are the representation of $\overline{\mathfrak{P}}$ and $\overline{\mathfrak{Q}}$, respectively. The matrix (K) is called sometimes as the "*ratio of the two fields*", or as the "*field angle from* $\overline{\mathfrak{P}}$ *to* $\overline{\mathfrak{Q}}$".[11),17),18)] The significance of this law of composition will be discussed as follows.

When the extensions of two fields $\overline{\mathfrak{P}}$ and $\overline{\mathfrak{Q}}$ in Π are equal, that is, when $[\overline{\mathfrak{P}}]=[\overline{\mathfrak{Q}}]$

$$\text{or} \qquad [p^1,\ p^2,\ldots\ldots p^n]=[q^1,\ q^2,\ldots\ldots,q^n] \tag{5-2}$$

holds, an equivalence relation such as $\overline{\mathfrak{P}} \equiv \overline{\mathfrak{Q}}$ (f) holds. Then, Π is classified by the relation (f), and a class in this classification is named particularly as a "*family*"[16)] in order to differentiate from the "*class*" in the classification by representation $\boldsymbol{P}^*$ (Fig. 5). When P^* and Q^* are the representations of respective two electric fields $\overline{\mathfrak{P}}$ and $\overline{\mathfrak{Q}}$ in the same family, $Q^*/P^*=(K)$,

$$\therefore \quad (Q)=(KP) \tag{5-3}$$

From formula (5-2), $\overline{Q}=(\mathcal{J})\overline{\boldsymbol{P}}$ $|\mathcal{J}|\neq 0$ holds. $\therefore$ $(Q)=(\mathcal{J}P)$ (5-4)

From formula (5-3) and (5-4), $(\mathcal{J})=(K)$ $\therefore$ $\overline{Q}=(K)\overline{\boldsymbol{P}}$ (5-5)

And from formula (2-13)', $p=A\cdot\overline{\boldsymbol{P}}$, $q=B\cdot\overline{Q}$ $(p \in \overline{\mathfrak{P}},\ p \in \overline{\mathfrak{Q}})$, $\therefore$ $q=B\cdot\overline{Q}=B\cdot(K)\overline{\boldsymbol{P}}=(K')B\cdot\overline{\boldsymbol{P}}$ Hence, $p=q$, if

"*Two electrocardiograms of respective two fields in the same family are equal, if the relationship* (5-6) *holds between field-position-coordinates of the respective two electrocardiograms.*"

To say in other words,

"*The ratio of the two fields,* $(K)=Q^*/P^*$, *may be regarded as a required quantity (transformation) in order to eliminate the "difference" between them.*"[17),18)]

This is the practical significance of the law of composition ω_1 defind in the

representation P^* of the electric fields. A more practical explanation of the field angle was reported before.[10]

If $\overline{\mathfrak{P}}$ and $\overline{\mathfrak{Q}}$ are not in the same family, the field $\overline{\mathfrak{R}}$ could be found in the same family with $\overline{\mathfrak{P}}$ (Fig. 5), and $R^*/P^*=Q^*/P^*=(K)$.

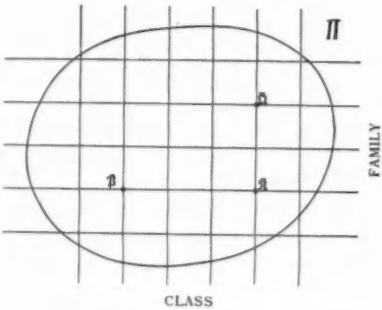

Fig. 2. Two sorts of classifications of the electric fields. The one is by representation (class), and the other is by extension (family).

Hence, if the relation (5-8) between field-position-coordinates A and C of p and r ($p\epsilon\overline{\mathfrak{P}}$, $r\epsilon\overline{\mathfrak{R}}$), respectively, $C=(K'^{-1})A$ (5-8)
holds, then $p=r$, $\therefore$ $P=R$ (5-9)

And as $Q^*=R^*$ from formula (5-7), $\overline{\mathfrak{Q}}$ and $\overline{\mathfrak{R}}$ are in the same class. When B is field-position-coordinate of $q\epsilon\overline{\mathfrak{Q}}$, and when Q and R are the bases of q and r, then, $Q=R$ holds if $B=C$. Hence, from formula (5-8) and (5-9), $P=Q$ holds if $B=(K^{-1})A$.

"*At least, the bases of two electrocardiograms of respective two fields are equal, if the relation* (5-6) *holds between field-position-coordinates of the two electrocardiograms.*"

The above is a discussion concerning ω_1 but another law of composition ω_2 defined as an addition, may be practically significant, although this is not so important here and omitted. Then,

"P^* *is a representation of* Π, *of two degrees.*"

It was mentioned that, in practical electrocardiography, the electric field had usually been represented by mean vector such as Einthoven's two-dimensional mean vector (frontal plane vector) and recently as spatial mean vector. According to our terminology in this chapter, Π has been represented in a two- or three-dimensional vector space. When representation of Π in three-dimensional vector space V_3 is V', $V'\subseteq V_3$ hols naturally. As $V_3\subset V_n$, where n is the dimension-number of the fields in $\overline{\Pi}$, $V'\subset V_n$. And as obviously $V_n\subset P^*$, $\therefore$ $V'\subset P^*$. Hence,

"*The representation of* $\overline{\Pi}$ *by the method of mean spatial vector is less strict than that by* P^*." or, "*The representation of* $\overline{\Pi}$ *by* P^* *is more strict than that by the method of mean spatial vector.*"

As to the significant laws of composition in V_2 or V_3, the two—addition and angle $\hat{A}_{PQ}$ between the mean vectors V_P and V_Q representing respectively $\overline{\mathfrak{P}}$ and $\overline{\mathfrak{Q}}$ in $\overline{\Pi}$ —are given usually. Thus, the respresentation V' is of two-degrees. The angle $\hat{A}_{PQ}$ is the law of composition which corresponds to the ratio of two fields (K) in our representation P^*. $\hat{A}_{PQ}$ is determined uniquely for given two vectors

V_P and V_Q, but conversely, V_Q is not determined even if V_P and $\hat{A}_{PQ}$ are given. For this reason, it may be better theoretically to give, as an law of composition ω_2, subtraction $V_P \omega V_Q = V_P - V_Q$ instead of the angle $\hat{A}_{PQ}$, if the practical point is not taken into consideration

Summary and Conclusion

(1) It is the author's opinion that the method of "mean spatial vector" has been introduced in order to compare several fields with each other and it has been efficient and available for that purpose. Every field is represented by its own mean spatial vector, and comparison of the vectors would make that of the fields possible. But it has been still unknown, how and to what degree the mean vector could represent the field, and what relation have the vectors representing the fields between each other. This problem of representation was generalized in this chapter.

(2) The set of equi-dimensional electric fields is represented by liner algebra composed of $n \times n$ matrices, when n is the dimension-number of the field. The algebra is a representation of the fields.

(3) Thus, the set of the fields has a finite-dimensional vector space as its homomorphic image.

(4) Hence, a field may be regarded as a vector in the homomorphic sense. *Electric Field is Vector.*

(5) When the field is represented by its own mean spatial vector, the field is regarded obviously as a vector. The above (4) is the result corresponding to this conventional view.

(6) The practical significance of law of composition in the representation was discussed, particularly the concept "ratio of two fields or field angle" was explained. The ratio of two fields may be considered as a required quantity (transformation) in order to eliminate the "difference" between these two, and may correspond to the angle between two mean spatial vectors of the respective two fields.

(7) The concept "more strict" representation was defined, and the degree of fidelity of the representation was taken into consideration. It was demonstrated that the representation by the algebra in (2) was more strict than that by the method of mean spatial vector.

(8) As to the application of the representation by the algebra, the author refers to their last reports.[17),18)]

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Case Report

Surgical Treatment of Aneurysm of the Aortic Arch
Report of Two Operated Cases with Synthetic Prostheses

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THE technique of resection and transplantation of the thoracic aorta, especially of the ascending aorta or the aortic arch has been behind the time because of its influence to the heart, problems concerning the cerebral circulation, spinal cord damages and difficulties of the technique itself. Since DeBakey et al.[1] reported operative methods for resection of aneurysm of the ascending aorta or the aortic arch with temporary bypass graft or with extracorporeal circulation, several cases of this kind of operation have been reported.[2]

Recently, 2 cases with aneurysms of the ascending aorta and the aortic arch have been operated with the use of prosthesis in our hospital and the cases will be herewith presented.

Case Reports

Case 1. A 49-year-old Japanese male was admitted to Tokyo University Hospital on January 27, 1960, with the chief complaints of chest pain, dyspnea and pressure feeling in left shoulder. Chest pain and pressure feeling of left shoulder were first noted in August 1959 and reappeared in January 1960. A year before the present admission, a routine chest X-ray film demonstrated an aneurysm of the thoracic aorta. Because of these symptoms he had to stay in bed for the most of the time.

About 30 years ago, the patient had syphilis and developed lymphogranuloma inguinale at the same time but did not have a series of antisyphilitic therapy.

On admission, the blood pressure was 130/100. Bilateral carotid pulses were normal to palpation. No thrill could be felt on the left anterior chest wall. Slight cardiac enlargement was noted and a soft apical systolic murmur was heard. No vocal cord paralysis was present. No venous distension was noted in the neck. The examination of the abdomen revealed no tenderness or rigidity. The liver, the spleen and the kidneys were not palpable, and there was no abnormal mass.

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On laboratory examinations, urinalysis was normal except for the positive urobilinogen, and routine blood works revealed no significant findings. Serological test for syphilis was positive. Total serum protein and A/G ratio were within normal limits and blood sedimentation rate was 42 mm. per hour. The liver function tests were normal and blood urea nitrogen was 40 mg. %.

Routine chest X-ray including posteroanterior and left lateral aspect revealed

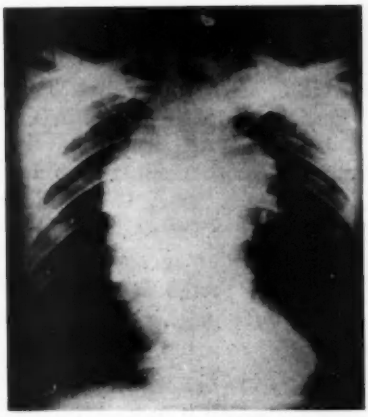

Fig. 1. Case 1. Preoperative chest X-ray showing an aneurysm of the aortic arch.

an aneurysm of the aortic arch (Fig. 1). This was confirmed by angiocardiography. There was no evidence of bony destruction. Retrograde aortogram through the right brachial artery showed an aneurysm involving the ascending and transvers portions of the arch.

On February 12, 1960, resection of the aneurysm was performed under general anesthesia, without hypothermia in patient supine position. Median sternotomy was done.

A large aneurysm involving the ascending aorta, the aortic arch and the middle part of the descending thoracic aorta was exposed.

Excision of the entire arch including the aneurysm with restoration of continuity by a graft seemed feasible. Further incision was made in the fourth intercostal space, forming a T-shape incision which gave excellent exposure of the entire aortic arch.

The pericardium was opened and the innominate, left carotid, and subclavian arteries were isolated and tapes were placed around these arteries. The left innominate vein was almost completely occluded where it crossed in front of the aneurysm, and it was ligated and severed twice. An aortic clamp was applied to the anterior wall of the ascending aorta.

End-to-side anastomosis was performed between a crimped Teflon tube, 20 mm. in internal diameter and 150 mm. in length, and the clamped area of proximal aorta. In the same way, anterior wall of the descending aorta was clamped and the distal end of the prosthesis was implanted to this clamped area (Fig. 2-a).

The ascending aorta was doubly clamped just distal to the shunt and severed. Upper end of the severed ascending aorta was sutured over and over with atraumatic needle. Cerebral blood flow was then maintained by way of the aortic shunt and retrograde way through the aortic arch to the brain (Fig. 2-b).

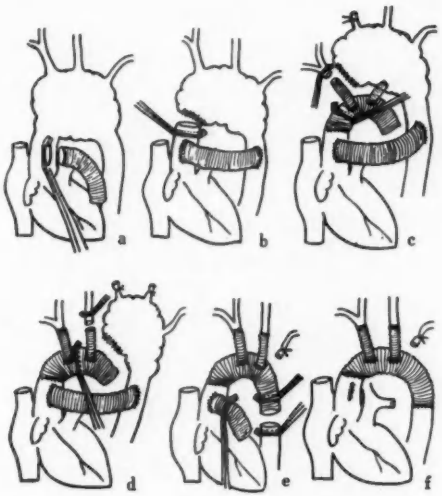

Fig. 2. Case 1. Operative procedure for resection of aneurysm of the aortic arch.

(a) End-to-side anastomosis was performed between the ascending aorta and bypass graft.

(b) End-to-side anastomosis was done between the descending aorta and the other end of bypass graft. The ascending aorta was severed above the former anastomosis.

(c) End-to-end anastomosis between the end of the ascending aorta and crimped Tetoron tube with branches.

(d) End-to-end anastomosis between the innominate artery and branch of the graft.

(e) End-to-end anastomosis between the left common carotid artery and another branch of the graft. The descending aorta was severed, and end-to-end anastomosis was done between the descending aorta and the graft.

(f) Bypass graft was removed. Transplantation was completed.

The reconstituted crimped Tetoron* tube, 19 mm. in an internal diameter, having 2 branches, 9.5 mm. in internal diameters was implanted into lower end of the severed ascending aorta and then one of the branches arising from the graft was anastomosed to the innominate artery (end-to-end) (Fig. 2-c).

The left common carotid artery was occluded and severed and then anasto-

* Tetoron: polyester fiber made in Japan.

mosed to another branch of the graft (Fig. 2-d). The noncrashing clamp was then moved to the area distal to the base of the left carotid branch of the graft, and thus normal fashion of blood flow in the carotid arteries was obtained. The left subclavian artery was simply ligated and severed.

The descending aorta distal to the bypass shunt was doubly clamped and severed. Then aneurysm was resected.

The anastomosis between the graft and the descending aorta was accomplished (Fig. 2-e), and after removal of the clamps normal blood flow through the aortic arch and its branches was established. The temporary bypass shunt was removed and the defect on the ascending aorta was closed by continuous suture with atraumatic arterial silk (Fig. 2-f, Fig. 3). During all these procedures E. K. G. and E. E. G. showed no remarkable changes (Fig. 4).

Fig. 3. Case 1. Transplantation with crimped Tetoron tube accomplished.

Tetoron graft with two branches was transplanted. End-to-end anastomoses were done between the graft and the ascending aorta, descending aorta, innominate and left common carotid arteries respectively. The left subclavian artery was ligated.

The opened pericardium was approximated roughly with silk suture. The thoracic wall was closed after insertion of Vinyl tubes into bilateral pleural spaces and mediastinum for water-seal drainage. The divided sternum was immobilized with wire sutures, the muscles and fascia were approximated with chromic catgut, and the skin was sutured with silk. A tracheotomy was performed to protect the patient from suffocation. About $8\,^1/_2$ hours were consumed for this operation. Blood loss was estimated to be 9,600 ml. and 10,400 ml. of whole blood was transfused

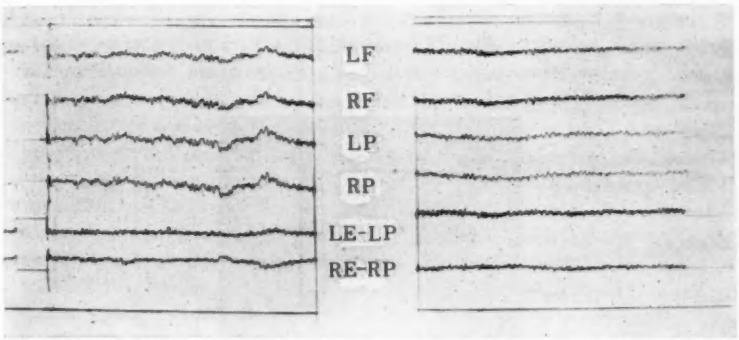

Fig. 4. Case 1. E.E.G. during operation for aneurysm of the aortic arch.

(left) During occlusion of the innominate artery. (Occluded for 15 minutes.)

(right) During occlusion of the left carotid artery. (Occluded for 20 minutes.)

No significant changes were noted in E.E.G. during occlusion of the innominate and left common carotid arteries.

Fig. 5. Case 1. Specimen of the resected aneurysm.

Resected aneurysm, 17×15×15 cm. in size. The outlets of the innominate, left common carotid and left subclavian arteries are shown. Copious blood clots filled the lumen.

during the procedure. Resected specimen is shown in Fig. 5.

The patient woke up promptly from anesthesia and there was no evidence of cerebral or spinal cord damages. The patient was mentally alert, and movement and sensation of legs were normal.

Excellent pulses were present in all peripheral arteries and vital signs were well maintained. His temperature was normal during and after the operation. Oliguria was not present after the procedure. Physical examination of the chest revealed both lungs to be well expanded.

On the second postoperative day, the mediastinum drain was removed, and the patient began to take a diet. Condition of the patient improved progressively. On the fifth postoperative day, pleural cavity drains were removed and a roent-

Fig. 6. Case 1. Chest X-ray after resection of the aortic arch. Abnormal shadow which was seen in the mediastinum preoperatively disappeared and showed relatively normal chest X-ray.

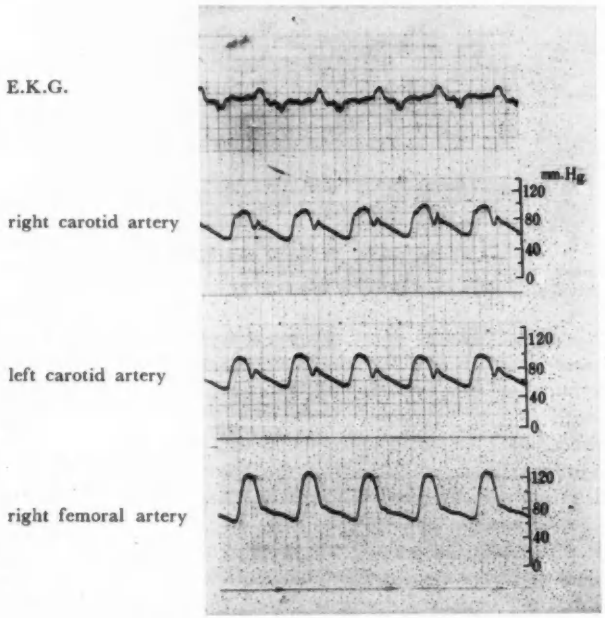

Fig. 7. Postoperative pressure curves of peripheral arteries.

genogram of the chest appeared satisfactory. The wound healed well and there was no evidence of infection of the wound. On the eighth postoperative day, digitoxin therapy was started because of the tachycardia. On the ninth postoperative day, tracheal cannula was removed. Dyspnea did not occur but his voice was very hoarse. Examination revealed left vocal cord paralysis. Ambulation was then started. On the twelfth postoperative day, the patient began to eat a regular diet without any difficulty. The E.K.G. was unchanged comparing with that of the preoperation. The postoperative chest X-ray revealed relatively normal finding (Fig. 6), and pressure curves in peripheral arteries taken on the twentyth postoperative day were nearly normal (Fig. 7). Laboratory findings revealed: hemoglobin 103% Sahli, hematocrit 50%, serum protein 6.6 Gm./100 ml., serum sodium 146 mEq./L., serum potassium 3.9 mEq./L., serum chloride 103 mEq./L.

The patient was discharged on March 14, 1960, the fourth postoperative week, in good condition physically and mentally. He has been well for about 1 year after the operation.

Case 2. A 68-year-old Japanese male was admitted to Tokyo University Hospital because of a huge pulsating tumor on the anterior chest wall. He had syphilis about 40 years prior to the present admission. He started to have pressure feeling in the anterior chest in March 1959 and noticed the tumor which had

Fig. 8. Case 2. Transplantation with crimped Tetoron tube accomplished.

Tetoron graft with three branches was transplanted and end-to-end anastomoses were done between the graft and the ascending aorta, innominate, left common carotid, left subclavian arteries and the descending aorta respectively. Circulation restarted and blood flow in each vessel was well maintained.

increased in size with aggravation of pressure feeling and finally he began to have hoarseness. In May 1959, diagnosis of aneurysm of the thoracic aorta was made. Since April 1960, the tumor had showed rapid increase in size and he developed slight dysphagia and neuralgia in the following month.

Aneurysm involving the ascending aorta and the aortic arch was diagnosed by chest X-ray. On May 25, operation was performed under general anesthesia. The aneurysm was resected with the same technique as case 1, and crimped Tetoron tube with 3 branches was transplanted (Fig. 8). Nine and a half hours were consumed for the operation. The patient remained unconscious and expired 12 hours after the operation. Cerebral ischemia or cerebral embolism provoked by clamping the carotid arteries was presumed to be the cause of the death. Autopsy revealed an embolus in right cerebral hemisphere.

Discussion

Two cases with aneurysm of the aortic arch have been presented. As stated before, resection of the thoracic aorta is quite difficult and many studies have been performed on this problem.

In case of the descending thoracic aorta, there are few problems

Table I. Experimental Results of Aortic Arch Transplantation in Dogs (Bypass Grafting with Crimped Teflon Tube)

No.	Sex	Body weight	Operative method	Results	Survival time	Cause of death
1	M	18.0Kg.	Bypass graft between the ascending and the descending aorta	Died		Haemorrhage
2	M	12.5	Same procedure as No. 1 plus closure of the ascending aorta	Alive	12 days	Insufficiency of suture
3	M	13.0	Same procedure as No. 1 plus resection of the aortic arch	Alive	6 days	do.
4	F	16.0	Bypass graft between the ascending and the descending aorta	Died		Cardiac insufficiency
5	M	15.0	do.	Died		Haemorrhage
6	M	15.5	do.	Died		Haemorrhage
7	M	13.0	Bypass graft and resection of the aortic arch	Alive	4 hours	Respiratory paralysis
8	M	16.0	do.	Alive	11 days	Insufficiency
9	F	14.0	do.	Alive	24 hours	Unknown
10	F	17.0	do.	Alive	3 days	Empyema
11	M	14.0	do.	Alive	3 hours	Respiratory Paralysis
12	M	16.5	do.	Alive	4 days	Insufficiency of suture
13	M	15.0	do.	Died		Haemorrhage

Note: Out of 13 cases, 8 cases (61%) were alive and 5 cases (39%) died during the operation.

Out of these 8 successful cases, 4 cases (50%) died of insufficiency of suture. The sites of insufficiency were all at the anastomosis on the ascending aorta.

concerning the cerebral circulation. However, spinal cord damages, and shock due to the ischemia of organs below the diaphragm are serious complications to be provoked by cross clamping.

To resolve these problems hypothermia and extracorporeal circulation have been applied with success so far by us,[8] but from our independent standpoint of view, we have devised a new "Cerebrospinal Fluid Draining

Table II. Cases with Surgical Treatment for Aneurysm of the Ascending Aorta and the Aortic Arch

No.	Name	Age	Sex	Diseased area	Note	Results
1	S.O.	55	M		Aneurysmorrhaphy	Died about 1 month after operation, because of the rupture of another aneurysm developed just above the site of aneurysmorrhaphy
2	K.F.	51	F		Only partial resection because of marked adhesion	Died immediately after operation (The left common carotid artery and the innominate artery were occluded.)
3	D.N.	55	M		Exploratory thoracotomy because of marked adhesion	Unknown
4	K.T.	44	M		Exploratory thoracotomy because base of the aortic arch was involved	Unknown
5	S.S.	51	F		Died of gross haemorrhage	Died during operation (Haemorrhage)
6	T.T.	56	M		Cardiac standstill immediately after starting left cardiac bypass	Died during operation (Cardiac standstill)
7	G.K.	62	M		Exploratory thoracotomy because of marked adhesion (Aorto-caval fistula was noticed)	Died on the first post-operative day (Impaired respiratory function)
8	T.K.	44	M		After transplantation of bypass graft, died of gross haemorrhage during separating adhesions	Died during operation (Haemorrhage)
9	Y.O.	56	F		After reconstruction of the aortic arch was accomplished, wall of the ascending aorta was injuried by cross clamping	Died during operation
10	H.M.	49	M		Presented in this report	Cured
11	T.H.	68	M		do.	Died of cerebral embolus 12 hours after operation

Method" and proved this method to be more excellent.[4]

Serious problems such as cerebral damages and myocardial damages must be considered when surgical treatment of aneurysm of the ascending aorta or the aortic arch is performed. Severing the neck of aneurysm and suturing the aneurysmal wall are one of the simple operative methods because it is unnecessary for this method to perform the aortic occlusion. In 1951, we reported a successfully operated case with this method.[5] According to this method, it is very possible that the recurrence of the aneurysm and the rupture may happen when diseased area of the aorta is left out.

It is now widely accepted that resection and transplantation of aneurysm is the best operative method. To perform this kind of radical operation, the helps with extracorporeal circulation or temporary bypass are needed. However, extracorporeal circulation is not thought to be preferable method because anticoagulant which must be used during extracorporeal circulation may aggravate the bleeding during the operation. We experimentally studied on temporary bypass method which was clinically applied by DeBakey et al. The results obtained were presented in Table I which proved the method to be excellent in spite of the difficulties of the technique. Until today operation has been tried on 11 clinical cases with aneurysms of the ascending aorta and the aortic arch including 2 cases reported here (Table II).

The operation of almost all cases in early period had not been accomplished because of the advanced lesions and difficulties of the techniques. Temporary bypass transplantation was applied to the recent cases and made it possible to perform resection and transplantation. However, for this type of the operation it is absolutely necessary that the temporary bypass is able to be placed to lateral wall of the ascending aorta proximal to the aneurysm. Consequently, it has a disadvantage when the whole area of the ascending aorta is involved in the aneurysm. In such a situation, extracorporeal circulation must be applied. Temporary bypass graft from the left ventricle to the descending aorta without using pump and anticoagulant is now being studied in our clinic.

Summary

Two cases of aneurysms of the ascending aorta or the aortic arch which were operated upon with resection and transplantation using temporary bypass grafting have been presented and operative methods for this kind of aneurysm have been discussed.

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